PERITONEAL ADHESIONS

risk and morbidity

Chema Strik

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Chapter 1

Introduction

Adhesion formation and adhesion-related complications

Peritoneal adhesions form in more than 90 percent of patients following open abdominal or pelvic surgery, which is predominantly performed by surgeons, gynaecologists and urologists.[1-3] Adhesion formation carries a huge clinical and socio-economical burden due to the lifelong risk for various clinical complications. Traditionally, intestinal obstruction, female infertility and chronic abdominal pain were regarded as the most important complications caused by adhesions.[4] In a recent systematic review and meta-analysis the incidence of reoperations for adhesive small bowel obstruction (ASBO) after abdominal surgery is estimated at 2.4 percent. The overall incidence of ASBO might actually be higher because presence of adhesions cannot always be confirmed in patients who had conservative management of their small bowel obstruction. The mean length of hospital stay after admission for an adhesive bowel obstruction is 7.8 days and in-hospital mortality is estimated at 2.5 percent.[4]

Pregnancy rate in female fertile-aged patients is 65 percent after colorectal surgery for inflammatory bowel disease surgery, which is significantly lower in comparison to medically treated patients who have a pregnancy rate of 82 percent. As many as 23 percent of these female patients seek fertility treatment after surgery.[4]

The incidence of chronic postoperative abdominal pain (CPAP) is estimated at 11 percent and is associated with a decrease in overall quality of life and an increase of gastro-intestinal symptoms.[5, 6] Adhesions and chronic abdominal pain often coincide after surgery, albeit their causative relationship has been debated due to the discrepancy between the incidence of adhesion formation and CPAP. Diagnosing adhesions as the cause of CPAP and gastrointestinal complaints is usually done per exclusionem. Nevertheless, in 57% of patients adhesions are deemed to be the cause of CPAP.[4]

While performing “pain mapping experiments” Demco et al found that touching and moving certain, but not all, adhesions caused a pain sensation in patients.[7] Additionally, a small follow-up study of a randomized controlled trial comparing the effectiveness of an adhesion barrier versus no treatment found that patients who received an adhesion barrier had less abdominal pain 10 years after surgery.[8] In contrast, a randomized controlled trial showed no additional benefit from laparoscopic adhesiolysis versus a diagnostic laparoscopy for patients with CPAP.[9] Establishing a more causative role between postoperative adhesions and CPAP can lead to renewed interest in this topic and improved treatment.

During repeat abdominal surgery, the need for adhesiolysis results in a 5.8% incidence of iatrogenic bowel injury, increased operative time of 15 minutes and a longer and more complicated convalescence.[4] The sequelae of iatrogenic bowel injury include unplanned bowel resection and the mortality rate is estimated at between 8 and 50 percent, depending on whether the injury was recognized during surgery.[10-12]

Due to a higher life expectancy and advances in surgical technology an increasing number of patients require abdominal surgery multiple times during their lifetime. The

rising life expectancy following abdominal surgery for benign and malign conditions, makes quality of life and socioeconomic costs an increasingly important outcome of elective abdominal surgery.[13-18] However, little is known of the impact of adhesiolysis-related complications on quality of life and socioeconomic costs. This information is important for patients undergoing elective surgery in giving informed consent, shared-decision making and to guide usage of adhesion barriers.

Prevention of adhesion formation

Part of the morbidity from postoperative adhesion formation might be preventable by using a surgical technique that minimizes peritoneal trauma and adhesion barriers. Good surgical technique remains difficult to substantiate. An important limitation of surgical technique, when used as the only means to prevent adhesions, is that the dissection areas and resection planes (in oncologic surgery) or the inserted materials (e.g. mesh and sutures in surgery for a ventral hernia) remain similar. However, there is some evidence that the incidence of adhesions and ASBO is lower after laparoscopic surgery in comparison to open surgery.[19]

Usage of an adhesion barrier is the next step in preventing peritoneal adhesion formation. Adhesion barriers work through separating injured peritoneal tissues and they are produced in various forms such as a solution, gel, spray or membrane. More than 20 different adhesion barriers have been investigated in clinical studies, many were either unsuccessful in reducing the formation of adhesions or were only assessed using outcomes of minor clinical importance.[20-22] A recent systematic review of 4 commercially available adhesion barriers demonstrated that these barriers were safe to use and two adhesion barriers showed modest benefits in reducing clinically relevant consequences of adhesions.[23] There is paucity in evidence regarding outcomes of clinical efficacy of adhesion barriers despite the extensive number of studies assessing adhesion barriers in the pre-clinical and clinical setting.

Although the burden of adhesions is high and the benefit of some barriers has been proven, these are seldom applied. In a nationwide survey in 2009 in The Netherlands only 13.4% of surgeons indicated to have used any adhesion barrier in the previous year.[24] Doubts about clear indications for appropriate usage and cost-effectiveness may explain the reluctance for using adhesion barriers. It is deemed unlikely that adhesion barriers will be cost-effective for patients undergoing all types of abdominal surgery.[25] Identification of sub-groups of patients more at risk for adhesion-related complications and patient-specific risk factors for adhesion-related complications might aid in establishing a tailored approach for usage of adhesion barriers in individual patients.

Risk factors for adhesion-related complications

The most frequent investigated adhesion-related complication is ASBO. The highest incidence is found after pediatric surgery and surgery of the lower gastrointestinal tract, however, it has not been elucidated why pediatric and colorectal surgery particularly harbour this risk.[4] One explanation is the longer life time risk, which is especially true for pediatric surgery. Another explanation, more applicable for colorectal surgery, is the extensive dissection which is needed causing adhesion formation between the remaining colon, small bowel, abdominal wall and, retroperitoneum. Such adhesion formation may compromise intra-abdominal bowel movement and increase the chance of the occurrence of an obstruction. This explanation is supported by the finding that a panproctocolectomy and total colectomy carry the highest risk for adhesion-related readmissions, with rates up to 30 percent.[26]

A completely non evidence-based explanation often given by surgeons is that a single adhesive band harbours a higher risk for bowel obstruction than multiple tenacious adhesions. In line with this opinion, some argue that usage of adhesion barriers might be dangerous due to incomplete prevention of postoperative adhesions thereby creating the possibility of patients ending up with single bands of abdominal adhesions.

In order to prevent adhesiolysis-related morbidity and guide adhesion barrier use, more knowledge of epidemiological patterns for repeat abdominal surgery is needed. Repeat abdominal surgery has only been investigated in a number of disease specific cohorts which assessed risk factors for undergoing reoperations for disease recurrence.[27, 28] However, repeat abdominal surgery might not be related to the index surgery, e.g. a sigmoid resection following previous hysterectomy. In this example the close proximity of these organs in the lesser pelvis can induce dense adhesions in the operative area causing significant risk during the second procedure. Two population based studies showed that the incidence of repeat abdominal surgery is 14 percent at two years after predominantly colorectal procedures and 36.7 percent at ten years after any type of abdominal surgery.[3, 29] Both studies lack patient-specific details and do not provide information regarding the indication or anatomical location of the repeat operation. Both are important to select patients at risk for repeat surgery and to optimize placement of a barrier at the right anatomical location after surgery.

Little is known about patient specific risk factors for the formation of peritoneal adhesions or adhesiolysis-related complications. Reported studies are small or of limited current relevance.[30, 31] The influence of the time interval between surgeries on the extent and severity of postsurgical adhesions is a topic of debate. Other risk factors that seem to impact the severity of adhesions are a history of peritonitis and presence of intra-peritoneal mesh.[2, 32-34]

Limited evidence suggests that the local expression of growth factors and proteins regulating fibrinolysis are increased in the peritoneum of patients with adhesions, potentially leading to aggravated adhesion reformation when lysed.[35, 36] Therefore, efficacy of adhesion barriers might be reduced if adhesions are already present during repeat abdominal surgery. This is supported by an animal study assessing the efficacy of repeated usage of adhesion barriers.[37] Improved knowledge of the effectiveness of adhesion barriers after repeat abdominal surgery could lead to more effective anti-adhesion strategies.
Combining patient-specific risk factors for adhesion-related complications and more effective usage of adhesion barriers could help to select patients that benefit most from adhesion prevention and thereby aid in effective anti-adhesion strategies.

Aim

The aim of this thesis is to determine the clinical impact of adhesiolysis. Secondary aims are the impact of adhesiolysis on the quality of life in abdominal surgery and to elucidate risk factors for short- and long-term complications of adhesiolysis and adhesions. The third aim is to assess the pre-clinical evidence regarding the prevention of adhesion reformation.

Outline

In **chapter 2** the current literature is reviewed regarding the pathophysiology of peritoneal inflammation, adhesion formation, sepsis and tumor growth. Injury to peritoneal mesothelial cells leads to an inflammatory response involving immunological, humoral, coagulation and neurological pathways interacting together in order to heal the injured surface.
In **chapter 3**, the results of a prospective cohort study of patients undergoing elective general abdominal surgery to assess the impact of adhesiolysis on postoperative morbidity, mortality and costs are presented. In 715 patients detailed data on adhesiolysis were gathered by direct observation during surgery. A comparison was made between surgical procedures with and without adhesiolysis.
In **chapter 4** the relationship between adhesiolysis and adhesiolysis-related complications and quality of life is assessed. 518 patients completed pre- and postoperative the Short Form-36 and Duke's Activity Status Index questionnaires and by using a multivariable regression analysis the impact of adhesiolysis on quality of life was assessed.
In **chapter 5** risk factors were assessed for the prevalence of postoperative chronic abdominal pain. 518 patients completed pre- and postoperative questions regarding pain and gastro-intestinal complaints. A multivariable regression analysis was performed to assess the relationship between the presence of adhesions, the need for adhesiolysis and postoperative pain and gastro-intestinal complaints.

In **chapter 6** risk factors are identified for prolonged and difficult adhesiolysis underneath the incision by analysing a prospective cohort of patients undergoing a repeat median laparotomy.
In **chapter 7** a nomogram is determined to assess the risk of the occurrence of an iatrogenic enterotomy during elective general abdominal surgery for individual patients.
A follow-up study of the prospective cohort in chapter 3 is presented in chapters 8 and 9. Patterns and risk factors for repeat abdominal surgery are described in **chapter 8**.
The incidence and risk factors of adhesive bowel obstruction was assessed in **chapter 9** with emphasis on the severity of adhesions and adhesiolysis data at initial surgery.
Available pre-clinical evidence regarding the prevention of adhesion reformation with anti-adhesive barriers is assessed by using systematic review and meta-analysis in **chapter 10**.
A general discussion and a summary of this thesis are presented in **chapter 11** and **chapter 12**.

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Chapter 2

Response to pathological processes in the peritoneal cavity - Sepsis, tumours, adhesions, and ascites

Martijn W.J. Stommel, MD, PhD[1], Chema Strik, MD[1], Harry van Goor, MD, PhD, FRCS
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
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[1] Both authors contributed equally to this article

Abstract

The peritoneum is one of the most common sites for pathological processes in pediatric surgery. Its response to pathological processes is characterized by an inflammatory reaction with specific pathways depending on the type of injury or peritoneal process involved. This review discusses the current understanding of peritoneal inflammation, adhesion formation, intra-abdominal sepsis, peritoneal metastasis, and ascites and briefly reviews new therapeutic strategies to treat or prevent these pathological entities. Recent studies have improved the understanding of the peritoneal responses to pathological processes, resulting in possible new targets for prevention and therapy.

Introduction

The peritoneal cavity is a confined space between the parietal peritoneum lining the abdominal wall, the retroperitoneum, and the visceral peritoneum covering the abdominal organs. Its total surface area is almost equal to the body surface area of the skin.[1] The peritoneum is a serous membrane of mesodermal origin, consisting of a monolayer of flat mesothelial cells anchored to the basement membrane. The subjacent connective tissue consists mainly of loose collagen fibers, including fibroblasts, blood and lymphatic vessels, as well as nerve fibers. The mesothelial cells play an active role in the physiological function as well as in pathological processes of the peritoneum. The peritoneal cavity contains less than 100 ml of serous fluid, an ultra-filtrate of plasma, which together with hyaluronan and a surfactant, produced by mesothelial cells, facilitates frictionless movement of the abdominal organs.[2] The peritoneum acts as a bidirectional semi-permeable membrane. The peritoneal mesothelial cells are interrupted by intermesothelial gaps (stomata of von Recklinghausen), which adapt to pathological conditions by retraction of the cell margins in response to pathological stimuli and in relation with diaphragmatic movements. At these stomata the peritoneal cavity is directly exposed to the extracellular matrix.[3] The action of the diaphragm generates a cephalad flow of peritoneal fluid through the stomata.[4] Under normal circumstances, approximately one-third of the peritoneal fluid drains through the diaphragmatic stomata into the main thoracic lymphatic ducts, the remainder exits through the parietal peritoneum.

The peritoneal defense mechanism can be triggered by various types of pathological processes “injuring” the peritoneum. Apart from (surgical) trauma, injury can be caused by invasive pathogens and tumor. The peritoneum responds to injury with an inflammatory reaction. This inflammatory reaction comprises four interacting pathways: immunological, humoral, coagulation, and neurological. In this article, we aim to give a comprehensive overview of the response to pathological processes in the peritoneal cavity.

General peritoneal response to injury

Injury of the peritoneum, whether surgical, inflammatory, or ischemic, causes a complex inflammatory reaction. This response has an integral role in wound healing and tissue repair to heal any sustained damage. The disruption of the cellular membrane, through apoptosis or necrosis, causes a release of intracellular molecules such as DNA, ATP, and IL-1α in the extracellular space.[5–7] These have been named as Damage-Associated Molecular Pattern molecules (DAMPs), but the mechanisms by which they generate an inflammatory response are not fully understood. The DAMPs induce a local cascade through activating receptors on mesothelial and local inflammatory cells. The mesothelial and local inflammatory cells produce chemoattractants (IL-8 and MCP-1), cytokines (TNF α, IL-1β, and IL-6), and growth factors (TGF β, IGF-1, and PDGF), which result in neutrophil extravasation which infiltrate the damaged area.[8]

Mast cells are abundantly present around bowel mucosa and are believed to play an important role in the inflammatory response of the peritoneum by inducing vasodilation through release of histamine. They can also be activated by DAMPs and activate several local immunological and endothelial cells and nerve fibers.[9] Neutrophils persist at the injured site for 1–2 days and are followed by monocytes recruited in the same manner; these differentiate into macrophages which contribute to the inflammatory reaction. The primary injury of the peritoneum not only leaves a denuded area with damaged mesothelial cells but also causes bleeding and extravasation of plasma proteins. Coagulation is up-regulated through the expression of tissue factor (TF) by macrophages and mesothelial cells. Interaction of TF with plasma proteins and thrombocytes forms a transient fibrinous matrix. The formation of an extensive fibrinous matrix is possible because the balance between coagulation and fibrinolysis is disturbed. The fibrinogen split products are known to promote pleural mesothelial proliferation, this might also be the case with peritoneal mesothelial cells.[10] Fibrinolysis, however, is decreased because there is an up-regulation of plasminogen activator inhibitor 1 (PAI-1) and a down-regulation of tissue-type plasminogen activator (t-PA). There is increasing evidence that inflammation and coagulation significantly affect each other. Coagulation is induced by inflammatory cytokines, while the coagulation-induced modulation of inflammatory activity is driven by specific cell receptors on inflammatory cells and endothelial cells.[7] Moreover, thrombocytes play their part in inflammation through storage and release of the pro- and anti-inflammatory factors TGF β and IL-1.[5] The neurological pathway of the inflammatory response of the peritoneum is activated by IL-1 binding to paraganglia cells. The “inflammatory reflex” is formed by signalling through afferent fibers of the vagus nerve to parasympathetic regions in the brainstem, leading to the release of neuropeptides from efferent nerve fibers and a resultant feedback on inflammation.[11] Different neuropeptides can lead to either anti-inflammatory (e.g., acetylcholine) or proinflammatory (e.g., substance P) effects on inflammation. While in the past resolution of inflammation has always been seen as a passive process, the discovery of locally acting mediators (pro-resolving mediators) has changed this view.[12] These proresolving mediators are produced via transcellular biosynthesis (i.e., between neutrophils and thrombocytes) and down-regulate the inflammatory reaction.

Adhesion formation

Healing of the injured peritoneum can result in the formation of peritoneal adhesions. As mentioned, injury of the peritoneum leads to a denuded surface with submesothelial damage evoking an inflammatory response. Simultaneously the coagulation cascade is activated and fibrin deposited at the site. A serosanguinous exudate rich in inflammatory cells, fibronectin, glycosaminoglycans, and proteoglycans is secreted through increased vascular permeability. This results in fibrin deposits that form an

adhesion between two formerly unconnected structures. Under normal circumstances, these fibrin deposits are degraded by fibrinolysis. This process of fibrinolysis is driven by the enzyme plasmin produced by macrophages and mesothelial cells. Plasmin is derived from its inactive substrate plasminogen by tissue-type plasminogen activator (t-PA) and urokinase-like plasminogen activator (u-PA). In its turn, t-PA is inhibited in its reaction by plasminogen activator inhibitor 1 (PAI-1) to keep the balance. However, peritoneal trauma leads to the absence of adequate fibrinolytic activity of the mesothelium and a mismatch in the fibrinolytic balance in favor of the persistence of fibrin clots.[13] Neighboring organs or the abdominal wall may adhere, generating a fibrin bridge between the attached tissues.[14] Under the actions of various cytokines, these fibrin bands are transformed into granulation tissue by the ingrowth of capillaries and fibroblasts and subsequently converted into permanent, collagenous, and highly organized tissue containing nerve fibers and vessels.

Adhesions frequently cause long-term complications after abdominal and pelvic surgery. After pediatric abdominal surgery, the incidence of adhesive small bowel obstruction can be as high as 15.6%, for example, after treatment of gastroschisis and omphalocele in neonates.[15,16] Other important clinical consequences of adhesions include infertility, chronic abdominal pain, malabsorption, and technical difficulties at reoperation. Many pharmacological methods and barriers have been used for adhesion prevention but only few have been proven to be successful. Prevention of adherence of adjacent structures by keeping them apart seems most efficacious. In a recent systematic review, the efficacy and safety of the four adhesion barriers approved for use in Europe and the USA were evaluated, showing evidence that membranes of oxidized regenerated cellulose and hyaluronate carboxymethylcellulose reduce adhesion formation.[17] Moreover, there is evidence that hyaluronate carboxymethylcellulose reduces the number of reoperations for adhesive small bowel obstruction. Evidence for efficacy on other clinically critical outcomes is lacking. Of the liquid adhesion barriers that are available in the market, icodextrin 4% solution is the most widely used. There is, however, limited evidence for the beneficial effect of icodextrin on the incidence of small bowel obstruction or other adhesion-related complications.[17,18]

An understanding of the pathological processes enables the modulation of the peritoneal environment and fibrinolytic capacity, which seems to harbor a therapeutic opportunity to prevent postsurgical adhesion formation. Intraperitoneal treatment with recombinant human plasminogen activator (rPA) was effective in preventing postoperative adhesion formation in experimental studies.[13] A pilot study in humans, however, showed no reduction of adhesions.[19] Since there was no measurable elevation of plasma t-PA level in the treatment group, this negative result was ascribed to too small a dosage. An interesting option to potentially combine anti-inflammatory, anti-coagulatory, and profibrinolytic properties is the use of statins. Beside their cholesterol-lowering capacity, there is accumulating evidence that statins effectively

lower plasma levels of CRP, have potent anti-inflammatory properties, and are effective stimulators of fibrinolytic activity by increasing t-PA and lowering PAI-1.[20,21] Also, the use of an angiotensin-II receptor blocker has potential efficacy in adhesion prevention through decreasing TGF β. The intraperitoneal administration of these agents alone and combined effectively reduced postsurgical adhesions in mice.[22] However, no data on efficacy in humans are available yet. Another potentially viable therapeutic target is substance P (a specific proinflammatory neuropeptide).[23] The effects associated with substance P are increasing inflammatory cytokine mRNA expression, stimulating angiogenesis, and proliferation of fibroblasts. This is mainly mediated through binding to neurokinin-1 receptor. Binding to the neurokinin-1 receptor can be inhibited through intraperitoneal administration of a neurokinin-1 receptor antagonist. In rats, interference with the actions of substance P with this antagonist showed early effects on the mRNA expression of several key mediators of adhesiogenesis.[24]

Intra-abdominal infection, abscess formation, and peritonitis

Intra-abdominal infection encompasses all forms of bacterial peritonitis, intra-abdominal abscesses, and infections of intra-abdominal organs. Perforation of a hollow organ is the leading cause of intra-abdominal infection, followed by postoperative peritonitis, ischemic damage of the bowel wall, infection of intra-abdominal organs, and translocation in nonbacterial peritonitis.[25]

Within minutes of bacterial invasion, a substantial proportion of the bacteria are absorbed from the peritoneal cavity through the stomata of von Recklinghausen in the diaphragmatic peritoneum and into the thoracic lymphatics.[26] At the same time, the bacteria activate the local response triggered by reaction of mesothelial cells and peritoneal macrophages, very similar to the response induced by sterile stimuli.[27] Chemoattractants, produced by mesothelial cells and local inflammatory cells, induce the recruitment of phagocytes (neutrophils and later macrophages), transmigrating from peritoneal capillaries to the mesothelial surface. Dilation of peritoneal blood vessels results in enhanced permeability, peritoneal edema, and the formation of protein-rich peritoneal exudates.[28] The local defense mechanism is able to localize and control the bacterial invasion through the formation of fibrinous adhesions trapping microbes and promoting local effector mechanisms to phagocytose them.[29] The omentum contributes to the overall localization process. The mesothelial cell layer of the omentum encloses two distinct types of tissue: an adipose-rich area and a thin translucent membranous area.[30] The adipose-rich area contains omental milky spots, consisting mainly of inflammatory cells. The translucent area has a net-like structure with multiple fenestrations, and its function is associated with regulating fluid transport. The fenestrations also facilitate adhesion of the omentum to damaged or inflamed organs, giving it motile properties. Once localized to the site of

contamination, the omentum acts to absorb microbes and contaminants through its stomata and secretes phagocytes through the milky spots. The omentum promotes healing via the local expression of growth factors and the stimulation of angiogenic activity.[31] An abscess forms when this localizing defense mechanism fails to completely clear the bacterial contamination. Such abscesses consist of bacteria, neutrophils, and necrotic debris walled off by a fibrinous or fibrous capsule termed pyogenic membrane. When viable bacteria are entrapped in the abscess wall or in the center, they cannot be reached by phagocytes and antibiotic therapy. This can result in bacterial proliferation[32] and, if overwhelmed, can lead to a systemic inflammatory response syndrome through the release of pro-inflammatory mediators (e.g., TNF α and IL-1) into the systemic circulation.[33]

The cornerstones of successful therapy in intra-abdominal infection are—source control, drainage of abscesses, and appropriate antibiotics. Very early antibiotic intervention is effective in reducing mortality in sepsis. Empirical use of antibiotics is often necessary when confronted by a sick patient and should be re-evaluated by local resistance surveillance.[34] The choice of the empirical antibiotic regimen should cover the intestinal flora, aerobes, and anaerobes. Examples of broad-spectrum antimicrobial regimens for pediatric patients with complicated intra-abdominal infection are an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase inhibitor combination (piperacillin–tazobactam or ticarcillin–clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole.[35] After surgically eliminating the source of abdominal infection in patients with severe abdominal sepsis, open abdomen should be avoided, since it leads to higher mortality.[36] An open abdomen is defined as a situation where the skin and fascia cannot be closed after laparotomy and the viscera are exposed, needing temporary closure or coverage techniques.[37] The only indication for open abdominal management is abdominal compartment syndrome, although even in this circumstance, temporary closure without tension is recommended. Planned re-laparotomy is not recommended and results in a higher mortality, a longer ICU and hospital stay, and higher costs when compared with an "on-demand" strategy of surgical re-exploration.[34,36]

Ascites

Ascites is a pathological state where an excess of fluid is accumulated within the peritoneal cavity. In approximately 80% of cases in adults, ascites is caused by hepatic cirrhosis. Other common causes include malignancy in 10% and heart failure in 3%.[38] Hepatic disorders are the most common cause of ascites in infants and children.[39] Three pathophysiologic processes contribute to the development of ascites in patients with cirrhotic liver disease: portal hypertension, vasodilation, and hyperaldosteronism. During the development of hepatic cirrhosis, the sinusoidal endothelial cells of the

intra-hepatic microcirculation fail to function, resulting in aberrant paracrine signalling. This process causes inflammation, fibrosis, and impaired vasomotor control, leading to increased intra-hepatic vascular resistance and portal hypertension.[40] Additionally, sinusoidal cells are highly permeable to albumin, making lymph formation dependent on hydrostatic forces alone, which are increased due to portal hypertension. A systemic effect of portal hypertension is vasodilation through increased nitric oxide production and hydrostatic pressure of the splanchnic circulation, leading to more fluid extravasation into the peritoneum. Furthermore, systemic vasodilatation results in relative hypovolemia and stimulates the renin–angiotensin–aldosterone system.[41] Increased antidiuretic hormone secretion induces water retention. While angiotensin normally promotes vasoconstriction, in the presence of hepatic cirrhosis, this effect is dampened.[42] If a patient develops hypoalbuminemia, a lower intra-vascular osmotic pressure exacerbates this process. An extensive summary of the different treatments for ascites due to cirrhotic liver disease goes beyond the scope of this review. In short, the intake of sodium should be restricted, and in most patients, addition of a diuretic is necessary. The most effective diuretic is spironolactone but a combination with furosemide might be required.[43,44] Paracentesis is a safe and effective treatment in the management of diuretic-resistant ascites.[45] If more than 5 l of fluid will be removed through paracentesis, intravenous albumin has been shown to improve survival.[46] A transjugular intra-hepatic porto-systemic shunt has shown to improve transplant-free survival in comparison to large-volume paracentesis.[47] Liver transplantation is a viable treatment in patients who develop diuretic-resistant ascites and early referral to a transplant center should be standard care.

In the presence of peritoneal malignancy, ascites has a completely different etiology. Malignant ascites develops because of a mismatch between filtration and drainage in the peritoneal cavity. In patients with peritoneal carcinomatosis, the cross-sectional area of microvessels that line the peritoneal cavity is increased.[48] Furthermore, due to the secretion of Vascular Endothelial Growth Factor (VEGF) by tumor cells, the permeability of microvessels is increased,[49] leading to an increased accumulation of protein-rich fluid in the peritoneal cavity. This shifts the oncotic pressure gradient further in the direction of the peritoneum. Impaired drainage from the peritoneum can also be caused by tumor cells blocking the peritoneal stomata, but this is a less important mechanism.[50] Due to the differences in etiology between malignant and cirrhotic ascites, diuretics are less effective in the treatment of malignant ascites. However, patients with extensive liver metastases might benefit from a diuretic.[51] Intraperitoneal chemotherapeutics, corticosteroids, cytokines, and a VEGF inhibitor have been reported to improve the control of ascites.[52–55] A randomized clinical trial using intraperitoneal administration of a monoclonal antibody, Catumaxomab, showed longer paracentesis-free survival and improved palliation in comparison to paracentesis alone.[56] Aflibercept, a VEGF inhibitor given intravenously, was evaluated in a phase 2,

double-blinded, randomized, placebo-controlled study also showed longer paracentesis-free survival, although this did not lead to an improved overall survival.[57] Complete resection of peritoneal metastasis is often not possible in patients with malignant ascites. Furthermore, the duration of postoperative recovery is comparable to the median overall survival time, making this patient category often considered ineligible for cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC).[58] Therefore, a laparoscopic approach with limited adhesiolysis and no cytoreductive surgery combined with HIPEC has been advocated. Due to its minimally invasive nature, this procedure has shown to be safe, and promising results with regard to palliation and overall survival have been reported.[59,60]

Peritoneal metastasis

Peritoneal metastasis is a common route for gastrointestinal malignancies, including appendiceal, colorectal, gastric, and pancreatic cancers. It is the primary metastatic route for ovarian malignancies. Peritoneal carcinomatosis is associated with a poor prognosis, irrespective of the primary origin of the tumor.[8,27] The process of intraperitoneal tumor dissemination differs from hematologic metastasis where tumor cells need to enter and exit the circulation and penetrate tissues. Peritoneal dissemination occurs in gastrointestinal malignancies when tumor cells exfoliate from the primary tumor after it has invaded the visceral peritoneum or in the case of a perforation of the gastrointestinal tract.[11] After dissemination into the peritoneum, tumor cells must prevent apoptosis and evade peritoneal clearance through the lymphatic system. This requires tumor cells to attach to the disrupted mesothelial surface or the exposed extracellular matrix (ECM) or at the stomata of von Recklinghausen for further disease progression. Tumor cells may adhere to the surface of mesothelial cells through various receptors[61–63] but show a predilection of adhering to type 1 collagen of the ECM.[64,65] The ECM is, therefore, the initial site of metastasis.[66] Surgical injury of the peritoneum exposes the ECM and damages the mesothelial cell layer.[67] Additionally, interactions between immune, mesothelial, and tumor cells create an inflammatory environment that causes the mesothelium to retract, exposing more of the ECM. Furthermore, inflammatory cytokines up-regulate mesothelial cell surface receptors enabling the attachment of tumor cells [68,69] and therefore increase metastatic spread. Tumor cells have the ability to assemble into multicellular aggregates, named spheroids, through direct cell–cell attachments.[70] When formed into spheroids, tumor cells have increased resistance against anoikis and chemotherapeutics.[71] Additionally, spheroid formation is associated with more invasive tumors.[72] Targeting spheroid formation by attenuating the contractile abilities of tumor cells might be an important treatment modality and is an area of extensive research.[73] The presence of ascites in patients with advanced ovarian cancer decreases their life expectancy when compared with patients who present without ascites in similar advanced ovarian

cancer.[74] Malignant ascites contains multiple growth factors and cytokines, [75–77] which enhance resistance against chemotherapeutic agents[78] and promote spheroid formation of tumor cells.[79] Increased amounts of fibrinogen and fibrin found in ascites may lead to the assemblage of tumor deposits that can become vascularized because of the presence of angiogenic growth factors.[80] Notably, heparin-binding epidermal growth factor (HB-EGF) has been shown to contribute to disease progression in ovarian cancer patients.[81] A small study reported promising results with an inhibitor of HB-EGF.[82]
The cornerstone in the treatment of peritoneal carcinomatosis, in the absence of other systemic metastasis, is complete cytoreductive surgery and HIPEC. Although associated with considerable morbidity and mortality, it has shown to improve overall survival. An important prognostic factor for survival is complete macroscopic tumor resection.[83,84]

Conclusion

The inflammatory reaction of the peritoneum forms an essential part of the physio-pathology of abscess formation, adhesion formation, malignant ascites, and peritoneal metastasis. Specific pathways and interactions depend on the type of injury to the peritoneum. An increased understanding of these pathological processes has yielded potential targets for new therapies.

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Chapter 3

Adhesiolysis-Related Morbidity in Abdominal Surgery

Richard P.G. ten Broek, M.D., PhD; Chema Strik, M.D.; Yama Issa, M.D., PhD;
Robert P. Bleichrodt M.D., PhD; Harry van Goor, M.D., PhD, FRCS
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
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Abstract

Objective: To determine the incidence of bowel injury in operations requiring adhesiolysis and to assess the impact of adhesiolysis on the incidence of surgical complications, postoperative morbidity, and costs.

Background: Morbidity of adhesiolysis during abdominal surgery seems an important health care problem, but the direct impact of adhesiolysis on inadvertent organ damage, morbidity, and costs is unknown.

Methods: In a prospective cohort study, detailed data on adhesiolysis were gathered by direct observation during elective abdominal surgery. Comparison was made between surgical procedures with and without adhesiolysis on the incidence of inadvertent bowel defects. Secondary outcomes were the effect of adhesiolysis and bowel injury on surgical complications, other morbidity, and costs.

Results: A total of 755 (out of 844) surgeries in 715 patients were included. Adhesiolysis was required in 475 (62.9%) of operations. Median adhesiolysis time was 20 minutes (range: 1–177). Fifty patients (10.5%) undergoing adhesiolysis inadvertently incurred bowel defect, compared with 0 (0%) without adhesiolysis ($P < 0.001$). In univariate and multivariate analyses, adhesiolysis was associated with an increase of sepsis incidence [odds ratio (OR): 5.12; 95% confidence interval (CI): 1.06–24.71], intra-abdominal complications (OR: 3.46; 95% CI: 1.49–8.05) and wound infection (OR: 2.45; 95% CI: 1.01–5.94), longer hospital stay (2.06 ± 1.06 days), and higher hospital costs [$18,579 (15,204–21,954) vs $14,063 (12,471–15,655)]. Mortality after adhesiolysis complicated by a bowel defect was 4 out of 50 (8%), compared with 7 out of 425 (1.6%) after uncomplicated adhesiolysis (OR: 5.19; 95% CI: 1.47–18.41).

Conclusions: Adhesiolysis and inadvertent bowel injury have a large negative effect on the convalescence after abdominal surgery. The awareness of adhesion-related morbidity during reoperation and the prevention of postsurgical adhesion deserve priority in research and clinical practice.

Introduction

Peritoneal adhesions develop after more than 90% of operations in the abdominal cavity, procedures frequently performed by general, vascular, and gynaecological surgeons and urologists.[1–3]

Intestinal obstruction, female infertility, and abdominal pain are well-known adhesion-related complications that negatively impact millions of lives worldwide.[1;2;4–7] Surprisingly, adhesion-related complications receive little attention in clinical practice.[8–11]

Complications that occur after adhesiolysis during repeat surgery might even form a larger burden of morbidity.[8] In a retrospective cohort, the risk of inadvertent bowel defects was as high as 19%.[12] The risk of needing repeat abdominal surgery is relatively high and is expected to increase in the western world with the increase of life expectancy and developments in surgical technology.[13–17]

Little is known of the impact of adhesiolysis and related organ injury on morbidity and socioeconomic costs in comparison with other adhesion-related complications. Knowledge of the morbidity related to adhesiolysis is needed to properly inform patients before surgery to take adhesiolysis risks into account in the operative decision-making, and to improve diagnosis of postoperative complications. In addition, proper data on adhesiolysis time and the socioeconomic burden of adhesions are helpful for operative room management and health care insurance.

In this prospective study, we did a detailed assessment and analysis of adhesiolysis, (post)operative complications, and socioeconomic factors in a large cohort of elective abdominal operations (clinicaltrials.gov registration number: NCT01236625).

Methods

Study Design and Patients

This was a prospective observational study as part of the LAPAD (LAParotomy or LAParoscopy and ADhesiolysis) study. The LAPAD study was designed to assess the incidence and impact of adhesiolysis on preoperative and postoperative complications, quality of life, and socioeconomic costs. All adult patients planned for elective abdominal surgery at the Department of Surgery of the Radboud University Nijmegen Medical Center between June 2008 and June 2010 were screened for inclusion. Patients planned for admission to the surgical day-care unit were excluded because the short hospital stay did not allow for adequate follow-up.

Inclusion criterion was an elective laparotomy or laparoscopy. Exclusion criteria were age under 18 years and mental disorder. Patients were included after giving oral and written informed consent.

Relevant patient, surgical, and medical data were prospectively assessed before, during, and after hospital stay and at the outpatient clinic until 6 months after discharge. At surgery, detailed information of adhesions, adhesiolysis, and inadvertent organ damage was collected through direct observation by a trained researcher (R.B., C.S.,

or Y.I.) who did not take part in the operation. Evaluation of adhesions was comprised of a description of the location, for example, ventral abdominal wall, operative area, and other parts of the abdomen, grading of adhesions at these 3 locations according to the Zühlke classification, and timing the duration of adhesiolysis by stopwatch.[18] Findings were recorded into the real-time database by the researcher present in the operating theatre. Operative and treatment decisions were made according to department guidelines or at the discretion of the surgical staff. As a rule in our institution, adhesiolysis was done by sharp dissection and not by electrocautery or ultrasonic dissection. The study was approved by the local medical ethical committee and conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul).

Variables

Primary outcomes were the incidence of adhesions, adhesiolysis time, the incidence of bowel defects, seromuscular injury, injuries to other organs and structures, and the incidence of major surgery-related complications.

A detailed description of any adhesion present was obtained by direct observation. Adhesiolysis time was measured in minutes from the start of adhesiolysis until the operative area was cleared of adhesions.

Bowel defects were classified as inadvertent enterotomy or delayed diagnosed perforation. Inadvertent enterotomy was defined as any iatrogenic, unintended full thickness bowel defect detected during operation. Preexisting fistulas or defects created while dissecting the bowel loop that harboured the fistula were not scored as inadvertent enterotomy. Delayed diagnosed perforation was defined as a bowel defect with spill of gastrointestinal content that was diagnosed postoperatively by imaging, at reoperation, or at autopsy, and that could not be explained by anastomotic leakage, bowel ischemia, or any other obvious causes of leakage unrelated to adhesiolysis.

Seromuscular injury was defined as injury to the serosal and muscular layers of the bowel, without visualization of the bowel lumen or spillage of bowel content. Other intraoperative injuries were comprised of any injury to the spleen, liver, pancreas, urogenital structures, lung, vascular structures, or nerves.

Postoperative complications noted as major surgery-related complications were death, wound infection (categorized as superficial or deep), anastomotic leak, fistula and abscess, pneumonia, sepsis, haemorrhage, and urinary tract infection. Major surgery-related complications were defined according to the criteria of the International Classification of Diseases, Tenth Revision, the National Nosocomial Infections Surveillance System, the Centre for Disease Control and Prevention, or according to the decision of the senior medical staff of the department.

Secondary outcomes were other morbidity and socioeconomic costs including total operative time, blood loss, recovery unit stay, hospital stay, unplanned or prolonged

intensive care unit admission, intensive care unit stay, parental feeding, tube feeding, incidence of emergency reoperations, and incidence of readmission to the hospital within 30 days after discharge.

Cost analysis was performed in United States dollars (unit of analysis) and included only the direct hospital costs: operation costs, ward stay, intensive care unit stay, extra charges for parental and tube feeding, postoperative diagnostics, reoperation costs, and blood products. Cost calculations were performed using the guidelines for cost analysis of the Dutch College of Health Insurance Companies using a top-down approach.[19] Operation costs were calculated based on total anaesthesia time using operating room costs of $1390 per hour, including personnel, material, and overhead costs. Total costs for the surgical ward and intensive care unit were $661 and $2289 per day, respectively, and included basic nutritional costs. More than basic parental and tube feedings were considered as extra nutritional costs. Diagnostic and reoperation costs were calculated using the 2004 price lists for medical procedures by the Dutch College of Health Insurance Companies. Medication costs and blood products costs were calculated according to the standardized price list of the Dutch College of Health Insurance Companies updated for June 2008.[20]

Baseline demographics included sex, age, body mass index, Alcohol Use Disorders Identification Test alcohol abuse index,[21] history of abdominal operations, number of laparotomies in history, number of laparoscopies in history, history of generalized peritonitis, American Society of Anaesthesiologists classification, P-Possum score, Revised Cardiac Risk Index, diabetes mellitus, extent of surgery, surgical approach (open or laparoscopic), anatomical site of operation [upper gastro-intestinal, lower gastro-intestinal, hepatobiliary–pancreatic, abdominal wall, or other], and level of surgical experience (surgeon or resident).

Statistical Methods

Univariate comparisons were performed using linear regression for continuous and logistic regression for dichotomous data. Effect size was expressed as mean difference with standard deviation for continuous data and odds ratios (ORs) for dichotomous data. Despite the large number of patients, differences in baseline factors between the groups were expected because adhesions are mostly due to prior surgery. To avoid potential bias by an unequal distribution of risk factors, we calculated an adjusted effect size using multivariate linear and logistic regression for continuous and dichotomous data, respectively. All factors with unequal distribution at baseline with $P < 0.010$ were included in the multivariate model, except a history of peritoneal surgery and generalized peritonitis, and peritoneal surgery and previous peritonitis were considered pathogenic for adhesion formation and were not expected to have further independent adverse effects on treatment outcomes. In composite outcomes, statistical results were presented for both the composite outcome and the

individual components of the composite. Costs are presented as mean cost with a 95% confidence interval (CI). Statistical comparison of costs was performed by multivariate regression on the logistically transformed values of the costs to reduce the impact of outliers. All outcomes were assessed per operation and analysed according to an intention-to-treat, unless otherwise stated.

In the subgroup of operations with adhesiolysis, we compared major surgery-related complications, other morbidities, and costs between adhesiolysis complicated by bowel defects and uncomplicated adhesiolysis.

In an additional analysis, we calculated the risk for enterotomy, seromuscular injury, and other organ injury by categorizing adhesiolysis time (none, 1–15, 16–30, 31–60, and >60 min).

There was only minimal missing data; thus, we excluded per analysis those cases with missing data. We used SPSS for Windows version 16.0 software (SPSS, Chicago, IL) for statistical analysis. Values of $P < 0.05$ were considered significant.

Results

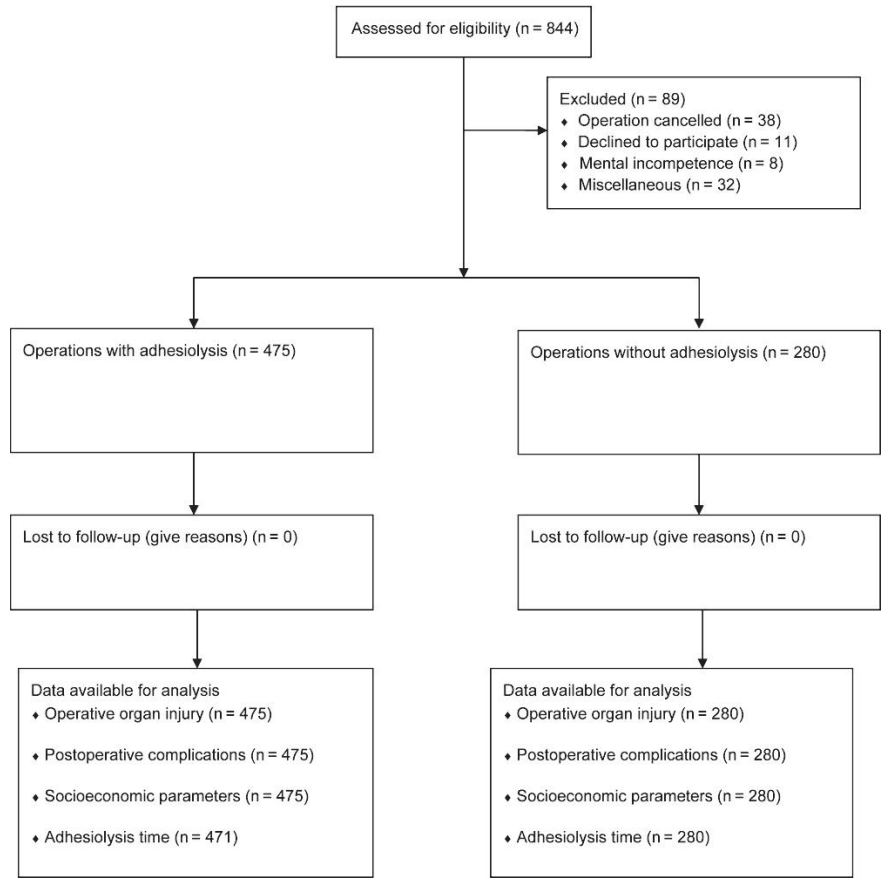
Cohort and Baseline Comparison

A total of 844 consecutive elective surgeries were screened for eligibility; 89 operations were excluded. Main reasons for exclusion were cancellation of the operation (N = 38), refusal to participate (n = 11), and mental incompetence of the patient (N = 8). A total of 755 operations carried out in 715 patients were included in the study (Figure 1). Adhesiolysis time was missing in 4 operations (0.5%). There were no further missing data.

The incidences of adhesions and adhesiolysis were 497 out of 755 (65.8%) and 475 out of 755 (62.9%), respectively. Most common etiologies for the presence of adhesions were previous intra-abdominal surgery and peritonitis (Table 1); mean adhesiolysis time was 20 minutes (range: 1–177). Adhesions to the incision scar of a previous operation were found in 399 (80.3%) of operations with adhesions, whereas in 416 operations (83.7%), adhesions were present in the operative area and in 329 operations (63.6%), adhesions were found in other parts of the abdomen. Median Zühlke score was 2 (range: 1–5) at all 3 locations. Severe adhesions (Zühlke score: 3 or 4) were found under a previous scar in 233 operations (46.9%) with adhesions, at the operative area in 235 operations (47.3%), and in other parts of the abdomen in 160 operations (32.2%). Patients who had adhesions and no prior surgery or general peritonitis in their history usually only had a few low-grade adhesions with a median adhesiolysis time of 5 minutes (range: 1–93). Those adhesions were mostly located adjacent to a local inflammatory process or tumour.

Table 1 shows the baseline data for the 2 groups. There were significant differences in the anatomical location of the operation ($P < 0.001$), operative severity ($P < 0.001$), surgical approach ($P = 0.01$), and body mass index ($P = 0.003$).

Figure 1 Flow diagram of the included operations.



Impact of Adhesiolysis on Peroperative Complications

The incidence of full thickness bowel defects was 10.5% in the adhesiolysis group and 0% in the nonadhesiolysis group ($P < 0.001$). During 43 operations, there was a median of 1 (range: 1–9) inadvertent enterotomy. Bowel resection and anastomosis were required in 24 operations (55.8%) with 1 or more enterotomies, and in the remaining operations, enterotomies were repaired by primary suturing. Injury to the seromuscular layer occurred in 131 procedures (27.6%) with adhesiolysis compared with 11 (3.9%) without adhesiolysis ($P < 0.001$). As a rule, seromuscular injuries were repaired by suturing.

Table 1 Baseline comparison between operations with and without adhesiolysis.

	Adhesiolysis group (n=475)	No adhesiolysis group (n=280)	P- value
Demographics			
Sex			
Male	264 (55.6%)	116 (59.3%)	
Female	211 (44.4%)	114 (40.7%)	.32
Age*	58.1 ± 13.8	59.4 ± 14.1	.23
BMI*	26.0 ± 4.8	25.1 ± 3.8	.003
Smoking status			
Non Smoker	163 (34.3%)	104 (37.3%)	
Ex- Smoker	210 (44.2%)	130 (46.6%)	.20
Smoker	102 (21.5%)	45 (16.1%)	
Alcohol abuse			
Low Risk	450 (94.9%)	261 (93.5%)	
Moderate Risk	18 (3.8%)	12 (4.3%)	.60
High Risk	6 (1.3%)	6 (2.2%)	
Peritoneal Surgery in History			
Yes	412 (86.7%)	90 (32.1%)	
No	63 (13.3%)	190 (67.9%)	<.001
Laparotomies in History†	2 (0-56)	0 (0-3)	<.001
Laparoscopies in History†	0 (0-2)	0 (0-1)	<.001
Generalized Peritonitis in History			
Yes	66 (13.9%)	1 (0.4%)	
No	409 (86.1%)	279 (99.6%)	<.001
Preoperative risk assessement			
ASA Slassification			
I	77 (16.2%)	46 (16.4%)	
II	284 (59.8%)	172 (61.4%)	
III	113 (23.8%)	62 (22.1%)	.83
IV	1 (0.2%)	0 (0.0%)	
P- Possum Score*	6.2 ± 9.8	6.0 ± 8.7	.79
Revised Cardiac Risk Index			
2	396 (83.4%)	222 (79.3%)	
3	66 (13.9%)	45 (16.1%)	.25
4	13 (2.7%)	13 (4.6%)	
Diabetes Mellitus in History			
Yes	43 (9.1%)	29 (10.4%)	
No	432 (90.9%)	251 (89.6%)	.56
Operative Severity			
Minor	0 (0.0%)	2 (0.7%)	
Moderate	22 (4.6%)	14 (5.0%)	
Large	311 (65.5%)	134 (47.9%)	<.001
Major	142 (29.9%)	130 (46.4%)	

Table 1 Continued.

	Adhesiolysis group (n=475)	No adhesiolysis group (n=280)	P- value
Characteristics of planned operation			
Open surgery/Laparoscopy			
Open surgery	440 (92.6%)	244 (87.1%)	
Laparoscopy	35 (7.4%)	36 (12.9%)	.01
Anatomical site of primary intervention			
Upper GI- tract	25 (5.3%)	58 (20.7%)	
Lower GI- tract	219 (46.1%)	122 (43.6%)	
HPB	82 (17.3%)	61 (21.8%)	
Abdominal wall	115 (24.2%)	9 (3.2%)	<.001
Other	34 (7.2%)	30 (10.7%)	
Surgical Experience			
Surgeon	330 (69.5%)	194 (69.3%)	
Resident	145 (30.5%)	86 (30.7%)	.96

Delayed diagnosed perforation occurred after 10 surgeries. A delayed diagnosed perforation occurred after 8 out of 142 seromuscular injuries (5.6%) and 3 out of 43 enterotomies (7.0%). The 3 patients with a delayed diagnosed perforation after an enterotomy also had seromuscular injuries. In 2 patients with delayed diagnosed perforation (20.0%), no seromuscular injury or enterotomy occurred during initial operation.

Injury to other organs was 8.6% in the adhesiolysis group compared with 2.5% in the nonadhesiolysis group (P = 0.001). Most common injuries in the adhesiolysis group were to the liver (n = 14), vascular structures (n = 11), urogenital structures (n = 8), spleen (n = 4), and bile ducts (n = 3). Injuries in the nonadhesiolysis group were comprised of vascular structures (n = 4), spleen (n = 2), and bile duct (n = 1).

After adjustment for anatomical location, operative severity, surgical approach, and body mass index, the difference in incidence of seromuscular injury and other organ injuries remained significant (Fig. 2A). Multivariate analysis could not be conducted for bowel defects as none occurred in the nonadhesiolysis group.

The 43 inadvertent enterotomies occurred exclusively in patients who underwent open surgery. One patient (2.9%) who underwent laparoscopy had a delayed diagnosed perforation compared with 9 (2.0%) who underwent open surgery (P = 0.75).

The incidence of enterotomy was 0.0% in virgin abdomens, 2.5% after 1, 8.7% after 2, and 15.5% after 3 or more prior abdominal operations. A high Zühlke score correlated with an increased incidence of enterotomy. Incidence of enterotomy was 0% in grade 1, 0.7% in grade 2, 8.9% in grade 3, and 36.4% in operations with grade 4 adhesions in the operative area. Enterotomies were found in 2 operations (0.6%) without adhesions to a previous scar, 0% with grade 1, 2.2% with grade 2, 12.0% with grade 3, and 26.9% with grade 4 adhesions to a previous scar. The correlation between adhesion grade and enterotomies was less strong for adhesions in other parts of the abdomen with an incidence of 0.5% without adhesions, 2.9% with grade 1, 7.4% with grade 2, 19.5% with grade 3, and 18.9% with grade 4 adhesions. The incidence of enterotomy, seromuscular injury, and other organ injury significantly increased with longer adhesiolysis time (Figs. 3A–C).

Impact of Adhesiolysis on Surgical Complications

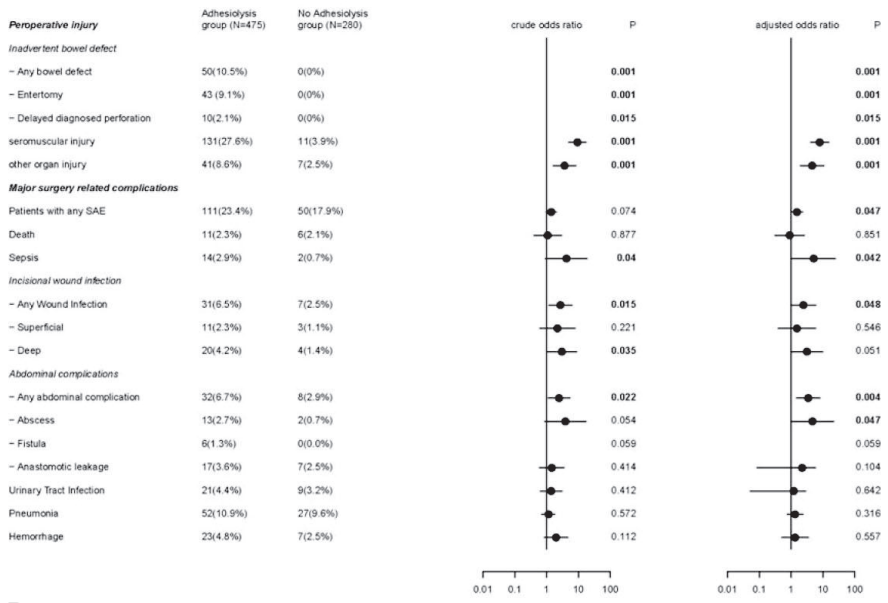
In the adhesiolysis group, 111 (23.4%) of surgeries had 1 or more major surgery-related complications compared with 50 (17.6%) in the nonadhesiolysis group [adjusted P = 0.05; (Fig. 2A)]. There was a significantly higher risk for sepsis, incisional wound infection, and abdominal complications in the adhesiolysis group (univariate analysis and after correction), although there were no significant differences in the incidence of death, urinary tract infection, pneumonia, or hemorrhage (Fig. 2A). The adjusted OR for sepsis was 5.12 (95% CI: 1.06–24.7), for wound infection 2.45 (95% CI: 1.01–5.94), and for abdominal complications 3.46 (95% CI: 1.49–8.05). Other variables included in multivariate analysis were not significant. Wound infections were found in 6 out of 67 operations (9.0%) performed with a history of peritonitis, compared with 32 out of 688 operations (4.7%) without peritonitis in their history—this difference was not significant (P = 0.137).

Impact of Adhesiolysis on Other Morbidity and Costs

Adhesiolysis was associated with a statistically significantly longer operative time, recovery time, and hospital stay. There was 29% more operative blood loss in the adhesiolysis group and more need of postoperative parental feeding. There tended to be more additional surgeries in the adhesiolysis group, although the difference was not significant (P = 0.060). Unplanned admissions to the intensive care unit and intensive care unit stays were comparable between the groups (Table 2).

Figure 2 **A**, Crude and adjusted ORs with 95% CI for (post)operative complications compared between surgery with and without adhesiolysis. **B**, ORs with 95% CI of postoperative complications after surgery with adhesiolysis compared between surgery with or without in advertent bowel defect.

A



B

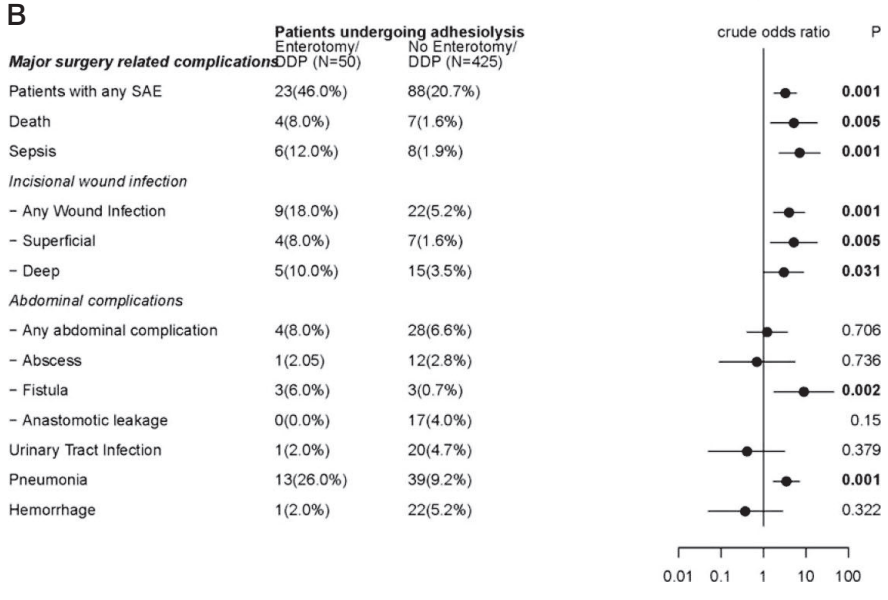
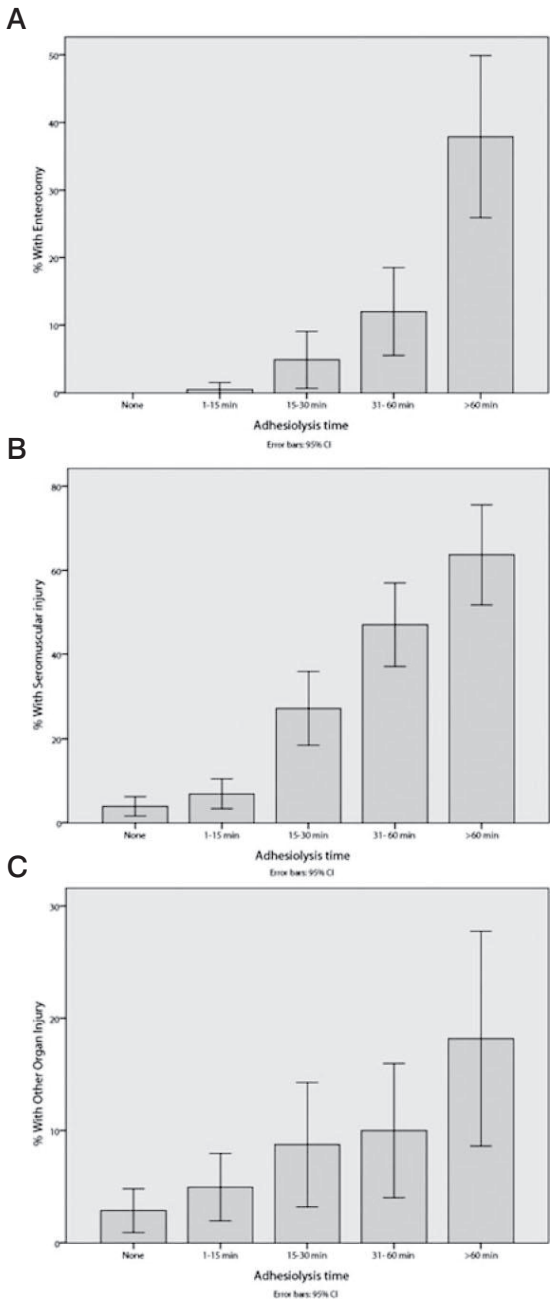


Figure 3 Risk of inadvertent organ injury with 95% CI stratified by adhesiolysis time: **A**, Enterotomy. **B**, Seromuscular injury. **C**, Other organ injury.



The inpatient costs were higher in the adhesiolysis group for all domains, resulting in a total of $18,579 (15,204–21,954) per operation for direct hospital costs compared with a total of $14,063 (12,471–15,655) in the nonadhesiolysis group ($P < 0.001$; Table 3). Readmission rate within 30 days after discharge was also significantly higher in the adhesiolysis group ($P = 0.002$). In the adhesiolysis group, 48 out of 69 readmissions (70.0%) were for a complication possibly related to previous surgery (abscess in 15, wound infection in 9, small bowel obstruction in 8, sepsis in 6, pneumonia in 5, and urinary tract infection in 5). In the nonadhesiolysis group, 12 out of 20 readmissions (60.0%) possibly were for a surgery-related complication (5 times for abscess, 2 times each for pneumonia, wound dehiscence, and leakage of the cervical anastomosis after esophageal resection, and once for urinary tract infection).

Impact of a Bowel Defect on Surgical Complications, Morbidity, and Costs

A major surgery-related complication occurred more than twice as often after adhesiolysis complicated by a bowel defect (Fig. 2B). The in-hospital mortality rate increased fivefold from 1.6% to 8.0% in the case of a bowel defect (Fig. 2B). The bowel defect group had significantly more additional surgical interventions ($P < 0.001$; Table 2). Hospital stay was a mean of 10.2 ± 2.4 days longer in the bowel defect group ($P = 0.036$). Total costs were almost threefold higher in patients with a bowel defect [$43,784 (16,629–70,938)] compared with those without a defect [$15,614 (13,642–17,586); Table 3].

Table 2 Morbidity Outcomes Compared Between Operations With and Without Adhesiolysis and Compared Between Surgery With or Without Inadvertent Bowel Defect in the Subgroup of Operations With Adhesiolysis; *= mean ± SD ; †= Unadjusted coefficient ± SD.

	Adhesiolysis group (n=475)	No adhesiolysis group (n=280)	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-Value	Enterotomy/ DDP (n=50)	No enterotomy/ DDP (N=425)	OR (95% CI)	P-value
Operation time (min.)	195 ± 98*	179 ± 89*	16.2 ± 7.1†	.020	22.5 ± 6.0†	<.001	221 ± 101*	192 ± 97*	29.5 ± 14.56†	.05
Blood loss (ml)	934 ± 1 630*	725 ± 905*	209 ± 106†	.024	305 ± 101†	.003	1 119 ± 1 438*	912 ± 1 652*	207 ± 244†	.35
Recovery unit stay (hours)	7.9 ± 10.9*	6.4 ± 9.0*	1.49 ± 0.77†	.043	2.21 ± 0.74†	.003	7.2 ± 8.8*	8.0 ± 11.2*	-0.8 ± 1.6†	.54
Hospital stay (days)	11.5 ± 16.5*	9.4 ± 8.5*	2.06 ± 1.06†	.024	3.14 ± 1.08†	.004	20.6 ± 33.1*	10.4 ± 12.8*	10.2 ± 2.4†	.04
Unplanned/ prolonged ICU admission	77 (16.2%)	51 (18.2%)	0.87 (0.59- 1.28)	.478	1.09 (0.70- 1.70)	.70	14 (28.0%)	63 (14.8%)	2.24 (1.14- 4.38)	.02
ICU stay (days)	1.9 ± 11.6*	1.0 ± 3.4*	0.94 ± 0.71†	.101	1.22 ± 0.73†	.10	9.3 ± 31.8*	1.08 ± 5.2*	8.25 ± 1.70†	.07
Parenteral feeding	77 (16.2%)	25 (8.9%)	1.97 (1.22- 3.18)	.005	2.00 (1.19- 3.34)	<.001	20 (40.0%)	57 (13.4%)	4.30 (2.29- 8.09)	<.001
Parental feeding (days)	3.0 ± 11.2*	1.4 ± 5.9*	1.58 ± 0.72†	.012	1.95 ± 0.74†	.009	11.7 ± 26.2*	2.0 ± 7.2*	9.73 ± 1.62†	.01
Tube feeding	95 (20.0%)	92 (32.9%)	0.511 (0.37 – 0.72)	<.001	0.99 (0.65- 1.49)	>.999	10 (20.0%)	85 (20.0%)	1.00 (0.48- 2.08)	>.999
Unplanned tube feeding	67 (14.5%)	44 (15.7%)	0.88 (0.58 – 1.33)	.546	1.09 (0.70- 1.70)	.21	10 (20.0%)	57 (13.4%)	1.61 (0.77- 3.41)	.21
Tube feeding (days)	3.3 ± 11.8*	3.55 ± 6.3*	-0.24 ± 0.76†	.718	0.47 ± 0.76†	.54	6.14 ± 23.7*	3.0 ± 9.5*	3.17 ± 1.76†	.35
Reoperations										
Any	74 (15.6%)	28 (10.0%)	1.66 (1.05	.030	1.62 (0.98	.06	16 (32.0%)	58 (13.6%)	2.98 (1.55	.001
Relaparotomy	57 (12.0%)	19 (6.8%)	1.87 (1.09	.021	1.68 (0.94	.08	13 (26.0%)	44 (10.4%)	3.04 (1.50	.001
Central Venous Line	11 (2.3%)	7 (2.5%)	0.93 (0.35	.873	1.13 (0.41	.81	1 (2.0%)	10 (2.4%)	0.85 (0.11	.88
Other	16 (3.4%)	6 (2.1%)	1.59 (0.62	.333	2.03 (0.67- 6.15)	.21	5 (10.0%)	11 (2.6%)	4.18 (1.39 – 12.58)	.006
Readmissions within 30 days of discharge	69 (14.5%)	20 (7.1%)	2.21 (1.31- 3.72)	.002	2.37 (1.36- 4.13)	.002	13 (26.0%)	56 (13.2%)	2.32 (1.16- 4.62)	.02

Table 3 Socioeconomical Cost Analysis Compared Between Operations With and Without Adhesiolysis and Compared Between Surgery With or Without Inadvertent Bowel Defect in the Subgroup of Operations With Adhesiolysis.

	Adhesiolysis group (n=475) mean(95% CI)	No adhesiolysis group (n=280) mean(95% CI)	P	Enterotomy/ DDP (n=50) mean(95% CI)	No Enterotomy/ DDP (N=425) mean(95% CI)	P
Operation cost	5204 (4986 – 5421)	4871 (4611 – 5131)	<.001	5 840 (5 143 – 6536)	5 129 (4 900 – 5358)	.03
Ward stay	6090 (5556 – 6624)	5438 (4894 – 5982)	.12	7 261 (5 719 – 8 804)	5 952 (5 383 – 6 522)	.04
ICU stay	4551 (2092 – 7009)	2349 (1405 – 3293)	.11	21 828 (648 – 43 007)	2 518 (1 350 – 3 686)	.006
Extra charges for parenteral/ tube feeding	945 (653 – 1237)	529 (331 – 727)	.93	3 411 (1 290 – 5532)	654 (453 – 856)	<.001
Medication	901 (451 – 1352)	382 (303 – 462)	.01	3 217 (0 – 7 196)	629 (427 – 832)	<.001
Diagnostics (radiology, pathology and microbiology)	475 (368 – 581)	400 (324 – 476)	.51	1 098 (350 – 1 846)	401 (321 – 481)	.13
Reoperations	177 (128 – 225)	94 (51 – 136)	.01	434 (181 – 746)	143 (100 – 186)	<.001
Blood products	274 (171 – 376)	99 (56 – 141)	<.001	811 (0 – 1 637)	211 (148 – 273)	.04
Total costs	18 579 (15 204 – 21 954)	14 063 (12 471 – 15655)	<.001	43 784 (16 629 – 70 938)	15 614 (13 642 – 17 586)	<.001

Discussion

In this study, adhesiolysis-induced morbidity was high: a median of 20 minutes increase of operative time, a 1 in 10 risk of inadvertent bowel defects, a sevenfold increase in seromuscular injury, and a threefold to fourfold increase in other organ injury. Adhesiolysis, particularly with the resulting bowel defects, led to more postoperative sepsis, intra-abdominal complications including surgical site infections, a longer hospital stay, more readmissions, and increased costs.

Adhesiolysis at repeat surgery has received less attention than bowel obstruction and infertility in reports assessing the clinical and socioeconomical burden of postoperative adhesions. Underestimation of the related morbidity and the passiveness of many physicians, who consider adhesiolysis an annoying but unavoidable part or redo surgery, account for the paucity of reports on the consequences of adhesiolysis. The available literature is limited to small series in specific surgical areas or retrospective series in which previous surgeries or rehospitalisation are taken as the measure of adhesiolysis.[2;12;22;23] We designed a large prospective study to provide accurate incidences of adhesiolysis-related morbidity and socioeconomical costs. This study provided for continuous observation of the surgical procedures in the operating theatre by a trained researcher who did not take part in the surgery. This enabled the collection of reliable data that most probably could not have been retrieved from other sources such as operative reports.[24–26]

The long total adhesiolysis time reflected the high complexity of these operations: when the adhesiolysis was longer than 1 hour, 40% of the operations resulted in bowel defects. Previous studies have used adhesion scores and entry times as the parameter for complexity.[18;23] However, an adhesion score is subjective and loses merit when adhesions are present in different parts of the abdominal cavity. Entry time is only a useful parameter when opening a previous abdominal incision and reflects a minor part of total adhesiolysis time and adhesiolysis-related complications.[12;23] We also had difficulty in distinguishing between adhesiolysis required just to enter the abdomen and adhesiolysis required to free the operative area in cases with massive adhesion formation to the ventral and lateral abdominal walls.

The incidence of inadvertent enterotomy in this study was lower than the 19% previously reported by our group.[12] The increased awareness of the impact of adhesiolysis and the modification in our department's protocol for cutting adhesions may have contributed to the decrease in bowel defects. Another explanation could be the strict definition of iatrogenic bowel defects, which no longer included enterotomies in the proximity of a pre-existing bowel fistula. The presence of an observer might also have raised the surgeon's vigilance to avoid injury. We noted, however, that the operating teams rapidly became accustomed to having an observer in the operating theatre.

The need for adhesiolysis in 60% of the surgical procedures and the low number of laparoscopies could limit the generalizability of the study results. However, these

percentages have been consistent in our academic department during the past decade, and they compare with those in a large multicentre series of patients who underwent elective colorectal surgery for a benign disease.[27;28] The percentage also results from the exclusion of short-stay surgery, which is predominantly minimally invasive surgery in virgin abdomens and emergency abdominal surgeries.

Our article is the first showing adhesiolysis as a risk factor for postoperative surgical complications, longer hospital stays, more readmissions, and increased costs. Inadvertent bowel defects increased even more morbidity and costs and they also caused significant mortality, which agrees with the results from our retrospectively collected data.[12;22] Incisional wound infection was the most prominent complication reflecting the longer adhesiolysis-related operating times and increased blood loss, events that are used to estimate the risk of surgical site infection.[29] The high morbidity, long hospital stay, and high costs of a surgical site infection are well known from other reports.[30;31] The portion of patients with surgical site infection after previous surgery could not be identified from the patients' medical charts. A history of peritonitis could be reliably obtained and was not a significant risk factor for surgical site infection.

The economical burden of adhesive bowel obstruction in the United States is at least 2 billion dollars annually.[32] The cost of adhesive small bowel obstruction per patient is estimated at $9700 for operatively treated patients and at $4000 for conservatively treated patients.[33;34] The cost data from this prospective study permitted an accurate calculation of the in-hospital costs related to adhesiolysis. These costs were $4500. Taking into account that adhesiolysis was required in 60% of the patients and that only about 2% to 4% of the patients acquire an adhesive small bowel obstruction after abdominal surgery, the economical burden of adhesiolysis is likely to exceed that of adhesive small bowel obstruction.[2;35] These cost calculations can be used for reimbursement purposes and to re-evaluate decisions concerning the use of barriers to prevent adhesion formation in elective abdominal surgery. Current cost-effectiveness analyses have focused on prevention of adhesive small bowel obstruction and, in many countries, have not lead to the routine use of anti-adhesive barriers.[33] With the projected increase in more repeat abdominal surgeries because of a longer life expectancy and newer technologies, prevention of adhesiolysis-related morbidity might be even more cost-effective.

The huge burden of adhesiolysis-related morbidity in elective abdominal surgery has consequences for the daily practice of physicians with regard to counselling patients. Less than 10% of surgeons inform their patients about the risk of adhesions.[9] The high risk of adhesiolysis complicating the immediate postoperative course warrants routine informed consent.[11] In an analysis of medicolegal claims for complications after adhesiolysis, inadvertent bowel injury accounted for a considerable portion of both submitted and granted complaints.[36;37]

This study has demonstrated the substantial clinical and socioeconomical burden of adhesiolysis, particularly when a bowel defect occurs. All physicians treating patients with disorders of the abdominal cavity that might require surgery should be aware of the adverse effects of adhesiolysis. Our data can be of help when counselling patients before surgery, when physicians and health care providers make decisions on implementing anti-adhesive strategies, and for the reimbursement policy of insurance companies.

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Chapter 4

Quality of life, functional status and adhesiolysis during elective abdominal surgery

Chema Strik, M.D.; Martijn W.J. Stommel, M.D., PhD; Jeroen C. Hol, M.D.;
Harry van Goor, M.D., PhD, FRCS; Richard P.G. ten Broek, M.D., PhD
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
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Abstract

Background: Adhesiolysis during abdominal surgery can cause iatrogenic organ injury, increased operative time and a more complicated convalescence. We assessed the impact of adhesiolysis and adhesiolysis-related complications on quality of life and functional status following elective abdominal surgery

Methods: Prospective cohort study, comparing patients requiring and not requiring adhesiolysis during an elective laparotomy or laparoscopy using the SF-36 and DASI questionnaire scores.

Results: 518 patients were included. Pre- and postoperative quality of life did not significantly differ between both groups. Patients with adhesiolysis had a significantly lower pre- and postoperative functional status ($p<0.01$). Higher age, concomitant pulmonary disease, postoperative complications, readmissions and chronic abdominal pain 6 months after surgery were all associated with a significant and independent decline in quality of life and functional status six months after surgery.

Conclusion and relevance: Adhesiolysis in itself does not affect functional status and quality of life six months after surgery. Postoperative complications, readmissions and chronic abdominal pain are associated with a lower health status.

Introduction

Quality of care in abdominal surgery is commonly measured by mortality and morbidity and seldom by quality of life or functional status.[1, 2] Due to the rising life expectancy following abdominal surgery, quality of life and functional status are becoming an increasingly important outcome of elective abdominal surgery.[3-7] Important mechanisms through which abdominal surgery affects quality of life and functional status are postoperative complications, a protracted convalescence and chronic postsurgical pain.[7-12] Most studies assessing quality of life after surgery focus on specific disorders, types of resection or anatomical reconstruction methods. These studies often lack a preoperative assessment of health status masking the impact of the operation on postoperative quality of life. Information on quality of life is important, especially for patients undergoing surgery for chronic diseases, in informed consent and shared decision making, and to evaluate patient reported treatment outcome.[2, 13-15]

Most patients who undergo repeat abdominal surgery have adhesions from previous operations and require adhesiolysis.[16] Adhesiolysis results in increased operative time and a longer and more complicated convalescence.[17] A 6-10% incidence of iatrogenic bowel injury during adhesiolysis is reported, increasing postoperative morbidity and mortality.[17, 18] Given the increased incidence of postoperative complications, it may be expected that adhesiolysis impairs quality of life and functional status, data to support this assumption are lacking. In the prospective LAPAD study adhesiolysis and related operative injuries have been assessed in detail for a variety of abdominal operations. Additionally, quality of life and functional status have been measured before and after surgery. Combined with a comprehensive assessment of baseline and postoperative data, the LAPAD database provides a unique opportunity to study the impact of both adhesiolysis and other factors on quality of life and functional status by an abdominal operation. In this prospective study the quality of life and functional status in patients requiring adhesiolysis was compared with patients who do not require adhesiolysis, while undergoing general abdominal surgery.

Methods

Study design and patients

This study was part of the LAPAD (LAParotomy or LAParoscopy and ADhesiolysis) study (clinicaltrials.gov registration number: NCT01236625). In the LAPAD study adult patients undergoing an elective laparotomy or laparoscopy at the department of surgery of the Radboud University Medical Center between June 2008 and June 2010 were included. Patients younger than 18 years or patients with a mental disorder were excluded. Detailed methods of the LAPAD study are published.[17] Relevant patient, surgical, and medical data were prospectively assessed before, during and after hospital stay and at the outpatient clinic until 6 months after discharge.

Patients who participated in the LAPAD study completed the Short Form 36 Health Survey (SF-36) and the Duke Activity State Index (DASI) the day before the operation.[19, 20] Six months after discharge the SF-36 and DASI questionnaire and a questionnaire regarding any readmissions was sent by regular mail. The SF-36 questionnaire measures overall quality of life and the DASI questionnaire functional status. Additional data was collected from medical records of hospitals, general practitioners and nursing homes when applicable. Patients who underwent a second elective abdominal operation that was included in the LAPAD study did not fill in a questionnaire before the second operation. Patients who did not complete the pre- or postoperative SF-36 and DASI questionnaires were excluded from analysis.

Variables

All baseline variables were defined according to the latest relevant guidelines and classifications. Medical history and complications were defined according to International Classification of Diseases, Tenth Revision, the National Nosocomial Infections Surveillance System, the Centre for Disease Control and Prevention. Baseline patient characteristics included sex, age, body mass index, smoking status, presence of pulmonary disease (comprising chronic obstructive pulmonary disease, asthma and emphysema), diabetes, renal failure, history of myocardial infarction, P-POSSUM score (Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and morbidity), presence of preoperative pain, presence of an ostomy (either colostomy or ileostomy) before surgery, the number of previous abdominal operations (none, 1 or 2, ≥3) and malignant disease, ventral hernia or other diseases as indication for surgery. Characteristics of the operation included surgical approach (open or laparoscopic) and anatomical site of the operation categorized as upper gastrointestinal tract, lower gastrointestinal tract, hepatobiliary-pancreatic, abdominal wall, or other. Other comprised retroperitoneal sarcoma resection, lymphatic and kidney resections as well as splenectomies and open abdominal aortic repair. Adhesiolysis time was measured in minutes from the start of adhesiolysis until the operative area was cleared of adhesions and was categorized as no adhesiolysis, 1-30 and >30 minutes adhesiolysis. The severity of adhesions underneath the previous incision and at the operative area were assessed using the Zühlke classification, comprising grade 0, 1 and 2 as no or mild adhesions and grade 3 and 4 as severe adhesions.[21] Adhesiolysis related complications were defined as either an enterotomy, serosal injury or other organ injury. Inadvertent enterotomy was defined as any iatrogenic, unintended full thickness bowel defect detected during operation. Preexisting fistulas or defects created while dissecting the bowel loop that harbored the fistula were not scored as inadvertent enterotomy. Serosal injury was defined as injury to the serosal and muscular layers of the bowel, without visualization of the bowel lumen or spillage of bowel content. Other organ injury was iatrogenic injury to other intra-abdominal organs including vascular

structures. All operative details were real-time collected by an independent observer present in the operating theater.

Postoperative complications during admission were classified using the Clavien-Dindo classification, combining complications with and without disability after discharge and combining complications grade 3a and 3b, and 4a and 4b due to the low incidence.[22] Chemotherapy received by patients was defined as any form of chemotherapy or no chemotherapy. Chronic abdominal pain was defined as occasional abdominal pain interfering with social activities 6 months after surgery or no abdominal pain.[23] Readmissions were categorized as any readmission within 30 days after discharge or between 30 days after discharge and 6 months after discharge.

The two endpoints are the quality of life and functional status based on total score of the SF-36 and DASI questionnaires 6 months postoperatively. The secondary endpoints are the subdomains of the SF-36.

Statistical methods

Baseline characteristics were compared between patients requiring or not requiring adhesiolysis using a Chi-square, Fisher's exact test, independent t-test or Mann-Whitney U test where appropriate. Continuous variables are presented as means with standard deviaton, or medians with interquartile range (25 – 75) if non-normal distribution. Dichotomous or categorical variables are presented as absolute numbers and percentages. A paired-samples t-test was used to compare the pre and postoperative quality of life scores. Variables having impact on quality of life and functional status scores 6 months postoperatively were determined using an univariable ANCOVA analysis with correction for baseline quality of life score.

All predictors $p = \leq 0.10$ in univariable analysis were considered for multivariable linear regression analysis. For the multivariable linear regression analysis, a stepwise backwards selection procedure was used with a probability of $F \leq 0.05$ and ≤ 0.10. The adjusted OR was calculated with 95 per cent confidence interval. A value of $p \leq 0.05$ was considered significant.

Additionally, all baseline variables with a significant impact on quality of life or functional status were compared between patients who completed both pre- and postoperative questionnaires and patients who only completed the pre-operative questionnaires but did not return the postoperative questionnaires.

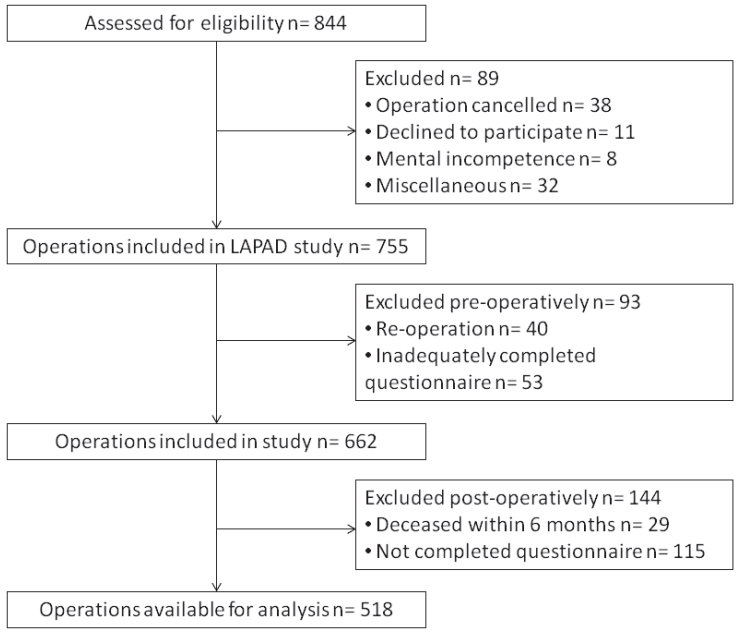
Cases with missing data were excluded per analysis. Statistical analysis was performed using SPSS statistical software package version 20.0 (SPSS Inc., Chicago, IL).

Results

715 patients, undergoing 755 operations were included in the LAPAD study. In 53 patients, pre-operative quality of life assessment was not available leaving 662 patients for inclusion. Six months postoperative data could not be captured in 144

patients, 29 patients died within 6 months and 115 patients did not return the post-operative questionnaires. Data of 518 (78%) patients were available for analysis of postoperative quality of life and functional status. A flow-chart is shown in figure 1.

Figure 1 Flow-chart.



Baseline characteristics

319 (62%) patients required adhesiolysis during surgery of which 110 patients required more than 30 minutes of adhesiolysis. A total of 158 (50%) patients had severe adhesions underneath the incision and 154 (49%) patients had severe adhesions at the operative area. In 29 (9%) patients requiring adhesiolysis an iatrogenic enterotomy occurred. A serosal injury occurred in 89 (28%) patients requiring adhesiolysis and in 8 (4%) patients who did not require adhesiolysis ($p = < 0.01$). At baseline, patients requiring adhesiolysis had significantly more often pre-operative abdominal pain ($p = <0.01$), more previous abdominal operations ($p = <0.01$), and had more often an abdominal wall repair for ventral hernia ($p = <0.01$). Patients requiring adhesiolysis had more Clavien-Dindo grade 1 ($p = 0.04$) and 4 ($p = 0.01$) complications and were more often readmitted within 30 days after discharge ($p = 0.01$). 199 (38%) patients

did not require adhesiolysis and underwent significantly more often an operation for a malignant cause ($p = <0.01$), and of the upper gastrointestinal and hepatic-pancreatic-billiary tract ($p = <0.01$). Baseline characteristics are shown in table 1.

Table 1 Baseline characteristics of patients requiring adhesiolysis and not requiring adhesiolysis during elective abdominal surgery.

Baseline characteristics (N = 518)			
Patient factors	**No adhesiolysis (n= 199)**	**Adhesiolysis (n=319)**	**p**
Sex			0.22
Male	120 (60%)	175 (55%)	
Female	79 (40%)	144 (45%)	
Age	60 ± 13	58 ± 13	0.06
BMI	25.4 ± 3.6	26.1 ± 4.8	0.12
Smoking status			0.14
Non-smoker	68 (34%)	117 (37%)	
Ex-smoker	103 (52%)	141 (44%)	
Smoker	27 (14%)	61 (19%)	
P-Possum score	3.0 (1.1 – 6.3)	1.80 (0.8 – 5.5)	0.36
Comorbidity			
Pulmonary disease	18 (9%)	32 (10%)	0.71
Diabetes	27 (14%)	36 (11%)	0.44
History of myocardial infarction	17 (9%)	19 (6%)	0.26
Renal failure	6 (3%)	10 (3%)	0.94
Pre-operative abdominal pain	50 (26%)	126 (39%)	<0.01
Number of previous abdominal operations			<0.01
0	138 (69%)	41 (13%)	
1 or 2	60 (30%)	154 (48%)	
≥3	1 (1%)	124 (39%)	
Presence of an ostomy before surgery	1 (1%)	51 (16%)	<0.01
Indication for surgery			
Malignancy	137 (69%)	106 (33%)	<0.01
Hernia	1 (1%)	95 (30%)	<0.01
Other	61 (30%)	122 (38%)	0.08
Surgical approach			0.02
Open	175 (88%)	299 (94%)	
Laparoscopic	24 (12%)	20 (6%)	
Anatomical site of operation			
Lower gastrointestinal tract	81 (41%)	138 (43%)	0.57
Abdominal wall	4 (2%)	86 (27%)	<0.01
Upper gastrointestinal tract	40 (20%)	14 (4%)	<0.01
Hepatic-pancreatic-billiary	47 (24%)	48 (15%)	0.01
Other	27 (14%)	33 (10%)	0.27

Table 1 Continued.

Baseline characteristics (N = 518)			
Patient factors	**No adhesiolysis (n= 199)**	**Adhesiolysis (n=319)**	**p**
Adhesiolysis time			<0.01
None	199 (100%)	0	
0 – 30 minutes	0	208 (65%)	
>30 minutes	0	110 (35%)	
Severity of adhesions underneath incision			<0.01
No, or mild adhesions	192 (99%)	161 (50%)	
Severe adhesions	0	158 (50%)	
Severity of adhesions operative area			<0.01
No, or mild adhesions	193 (100%)	161 (51%)	
Severe adhesions	0	154 (49%)	
Adhesiolysis related complications			
Enterotomy	0	29 (9%)	<0.01
Serosal injury	8 (4%)	89 (28%)	<0.01
Other organ injury	4 (2%)	32 (10%)	<0.01
Creation of an ostomy			
Colostomy	16 (8%)	20 (6%)	0.21
Ileostomy	19 (10%)	43 (14%)	0.45
Number of patients with complications			
Clavien-Dindo grade 1	24 (12%)	60 (19%)	0.04
Clavien-Dindo grade 2	37 (19%)	80 (25%)	0.09
Clavien-Dindo grade 3	27 (14%)	48 (15%)	0.64
Clavien-Dindo grade 4	1 (1%)	13 (4%)	0.01
Readmissions during follow-up			
Readmission within 30 days	18 (9%)	54 (17%)	0.01
Readmission after 30 days	31 (16%)	45 (14%)	0.70
Chemotherapy during follow-up	45 (25%)	34 (13%)	<0.01
Postoperative abdominal pain 6 months after surgery	66 (33%)	118 (37%)	0.36

The 115 patients who did not return the questionnaire six months after surgery were significantly younger (p = 0.02) and smoked more often (p = <0.01). The baseline characteristics of the non-responders are shown in table 2.

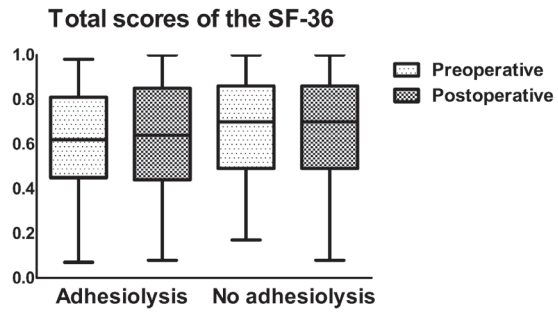
Table 2 Characteristics of patients having returned and not having returned the questionnaire 6 months after abdominal surgery.

Characteristics non-responders			
Patient factors	**Responders (n= 518)**	**Non-responders (n= 115)**	**p**
Sex			0.67
Male	295 (57%)	63 (55%)	
Female	223 (43%)	52 (45%)	
Age	58 ± 13	55 ± 17	0.02
Smoking status			<0.01
Non-smoker	185 (36%)	34 (30%)	
Ex-smoker	244 (47%)	46 (40%)	
Smoker	88 (17%)	35 (30%)	
P-Possum score	2.3 (0.9 – 5.8)	2.40 (0.9 – 6.7)	0.66
Comorbidity			
Pulmonary disease	50 (10%)	16 (14%)	0.18
History of myocardial infarction	36 (7%)	7 (6%)	0.74
Indication for surgery			0.40
Malignancy	243 (47%)	49 (43%)	
Surgical approach			0.07
Open	474 (91%)	99 (86%)	
Laparoscopic	44 (9%)	16 (14%)	
Anatomical site of operation			0.20
Lower gastrointestinal tract	219 (42%)	62 (54%)	
Abdominal wall	90 (17%)	17 (15%)	
Upper gastrointestinal tract	54 (10%)	9 (8%)	
Hepatic-pancreatic-billiary	95 (18%)	19 (17%)	
Other	60 (12%)	8 (7%)	
Requirement adhesiolysis			0.58
Yes	319 (62%)	74 (64%)	
No	199 (38%)	41 (36%)	
Adhesiolysis related complications			
Serosal injury	97 (19%)	22 (19%)	0.92
Number of patients with complications			
Clavien-dindo grade 2	117 (23%)	35 (30%)	0.08
Clavien-dindo grade 3	75 (15%)	15 (13%)	0.69
Clavien-dindo grade 4	14 (3%)	2 (2%)	0.75
Readmissions during follow-up			
Readmission within 30 days	72 (14%)	16 (14%)	1.00
Readmission after 30 days	76 (15%)	22 (19%)	0.25
Preoperative SF36 score	0.64 (0.46 – 0.84)	0.57 (0.42 – 0.80)	0.06
Preoperative DASI score	32.20 (20.70 – 50.70)	31.45 (15.45 – 50.70)	0.30

Pre- and postoperative quality of life and functional status

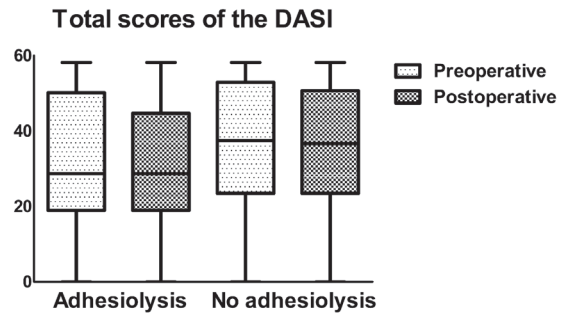
The results of the SF-36 score are shown in figure 2. A trend was seen towards a lower preoperative quality of life for patients requiring adhesiolysis in comparison to patients not requiring adhesiolysis (p = 0.05). Postoperative quality of life did not significantly differ between both groups (p = 0.12). Quality of life 6 months after surgery was comparable to preoperative quality of life in both patient groups (p = 0.43 and p = 0.82, respectively). The preoperative physical functioning, physical role and bodily pain subdomains of the SF-36 were significantly lower for patients requiring adhesiolysis during surgery, whereas the mental health subscale was significantly higher for patients requiring adhesiolysis. Postoperatively, only physical functioning was lower for these patients. Both groups showed significantly improved mental health and reduced general health after operation (results not shown).

Figure 2 Total pre- and postoperative SF-36 scores for patients requiring adhesiolysis and patient without requiring adhesiolysis. The box-plot represents the median, IQR 25 – 75 and the range. The SF-36 scores for the adhesiolysis group were 0.62 (0.45 – 0.81) preoperatively and 0.64 (0.44 – 0.85) postoperatively. The no adhesiolysis group had a preoperative SF-36 score of 0.70 (0.49 – 0.86) and a postoperative score of 0.70 (0.49 – 0.86).



Patients requiring adhesiolysis had a significantly lower pre- 28.70 (18.95 – 50.20) and postoperative 28.70 (18.95 – 44.7) DASI score in comparison to the pre- 37.45 (23.45 – 52.95) and postoperative 36.70 (23.45 – 50.70) DASI score of patients not requiring adhesiolysis (p = <0.01 and p = <0.01) (figure 3). Change of functional status in both groups of patients was not significant (p = 0.36 and p = 0.22, respectively).

Figure 3 Total pre- and postoperative DASI scores for patients requiring adhesiolysis and patients not requiring adhesiolysis. The box-plot represents the median, IQR 25 – 75 and the range. The DASI scores for the adhesiolysis group were 28.70 (18.95 – 50.20) preoperatively and 28.70 (18.95 – 44.7) postoperatively. The no adhesiolysis group had a preoperative DASI score of 37.45 (23.45 – 52.95) and a postoperative score of 36.70 (23.45 – 50.70).



Impact of patient factors on quality of life

Higher P-Possum score, concomitant pulmonary disease, presence of an ostomy, serosal injury during the operation, postoperative complications Clavien-Dindo grade 2, 3 and 4, readmissions within and after 30 days and chronic abdominal pain all negatively impacted quality of life six months after surgery. A laparoscopic procedure, lower gastrointestinal tract as the anatomical location of surgery and a higher preoperative SF-36 score had a positive impact on quality of life. The results of the univariable analysis are shown in supplement 1.

In the multivariable analysis (table 3), higher age (95% CI -0.00 – -0.00; p 0.04), concomitant pulmonary disease (95% CI -0.11 – -0.00; p 0.04), postoperative Clavien-Dindo grade 4 complications (95% CI -0.25 – -0.05; p <0.01), readmission within 30 days (95% CI -0.11 – -0.02; p 0.01), readmissions after 30 days (95% CI -0.12 -0.03; p <0.01) and chronic abdominal pain 6 months after surgery (95% CI -0.18 – -0.11; p <0.01) were all associated with a significant and independent decline in quality of life six months after surgery. Patients that underwent surgery on another anatomical site than the lower or upper gastrointestinal tract, hepatic-pancreatic-biliary tract or the abdominal wall were associated with a reduced quality of life (95% CI -0.13 - -0.03; p <0.01). A trend was seen towards impaired quality of life six months after surgery where a serosal injury occurred during surgery (95% CI -0.08 – 0.01; p 0.10). Laparoscopic approach (95% CI 0.00 – 0.12; p 0.04) and a higher preoperative SF-36 score (95% CI 0.36 – 0.51; p <0.01) were associated with improved quality of life after surgery.

Table 3 Multivariable analysis for patient factors impacting the postoperative SF-36 score.

Patient factor	B	Standard error	95% confidence interval		P
			Lower	Upper	
Age	- 0.00	0.00	- 0.00	0.00	0.04
Comorbidity					
Pulmonary disease	- 0.06	0.03	- 0.11	- 0.00	0.04
Laparoscopic approach	0.06	0.03	0.00	0.12	0.04
Anatomical site of operation					
Lower gastrointestinal tract	Not included				
Abdominal wall	Not included				
Upper gastrointestinal tract	Not included				
Hepatic-pancreatic-billiary	Not included				
Other	- 0.08	0.03	- 0.13	- 0.03	<0.01
Adhesiolysis-related complication					
Serosal injury	- 0.04	0.02	- 0.08	0.01	0.10
Postoperative complications					
Clavien-Dindo grade 4	- 0.15	0.05	- 0.25	- 0.05	<0.01
Readmission					
Within 30 days after discharge	- 0.06	0.02	- 0.11	- 0.02	0.01
After 30 days after discharge	- 0.07	0.02	- 0.12	- 0.03	<0.01
Postoperative abdominal pain 6 months after surgery	- 0.14	0.02	- 0.18	- 0.11	<0.01
Preoperative SF-36 score	0.44	0.04	0.36	0.51	<0.01

Impact of patient factors on functional status

Higher age, smoking, higher P-Possum score, concomitant pulmonary disease, history of myocardial infarction, malignancy as indication for surgery, postoperative complications Clavien-Dindo grade 2, 3 and 4, readmissions within and after 30 days and chronic abdominal pain were all associated with a decline in functional status of patients six months after surgery in the univariable analysis. A laparoscopic procedure and a higher pre-operative DASI score was associated with an increased functional status six months after surgery. The results of the univariable analysis are shown in supplement 2.

In multivariable analysis (table 4) higher age (95% CI -0.34 - -0.17; p <0.01), concomitant pulmonary disease (95% CI -9.53 - -2.30; p <0.01), postoperative Clavien-Dindo grade 4 complication (95% CI -13.07 - -0.16; p 0.05), readmission within 30 days (95% CI -7.44 - -1.39; p <0.01), readmissions after 30 days (95% CI -9.08 - -3.23; p <0.01) and chronic abdominal pain 6 months after surgery (95% CI -8.72 - -4.15; p <0.01)

were all associated with a significant and independent decline in functional status 6 months after surgery. A higher preoperative DASI score (95% CI 0.47 – 0.59; p <0.01) was significantly associated with a higher postoperative functional status (table 4).

Table 4 Multivariable linear regression analysis of patient factors impact on postoperative functional capacity of patients.

Patient factor	B	Standard error	95% confidence interval		P
			Lower	Upper	
Age	-0.25	0.04	- 0.34	- 0.17	<0.01
Comorbidity					
Pulmonary disease	- 5.92	1.84	- 9.53	- 2.30	<0.01
Postoperative complications					
Clavien-Dindo grade 4	- 6.61	3.29	-13.07	- 0.16	0.05
Readmission					
Within 30 days after discharge	- 4.41	1.54	- 7.44	- 1.39	<0.01
After 30 days after discharge	- 6.16	1.49	- 9.08	- 3.23	<0.01
Postoperative abdominal pain 6 months after surgery	- 6.44	1.16	- 8.72	- 4.15	<0.01
Preoperative DASI score	0.53	0.03	0.47	0.59	<0.01

Discussion

In this large cohort study of surgical patients, data are provided regarding the impact of adhesions on patient reported outcomes. Almost two-third of patients needed adhesiolysis as part of the surgical procedure. They reported a lower functional status both before and after operation but adhesiolysis independently did not affect quality of life or functional status. Irrespective of adhesiolysis, major complications, readmissions and chronic abdominal pain have a large negative impact on quality of life and functional status. Six months after surgery, patient reported outcomes were comparable to preoperative values. High preoperative functional status and quality of life were associated with better postoperative outcomes.

Patients needing adhesiolysis at repeat abdominal surgery represent a surgical population with a lower level of physical functional performance compared to patients having their first abdominal operation or having insignificant adhesions. The lower performance pre-operatively in the adhesiolysis group may relate to the higher percentage of patients with preoperative abdominal pain, other consequences of their previous conditions and surgeries and the indication for their current operation.

Chronic pain is a known denominator of quality of life and physical functioning in particular. One third of all patients reported abdominal pain six months after surgery, this percentage is comparable to the literature.[11, 17, 24] Abdominal (and pelvic) pain is an increasingly recognized long term surgical complication, is more common in patients with preexisting pain and after open lower gastrointestinal surgery and ventral hernia repair, which constitute the most frequent operations in our series.[11, 25] In comparison with baseline measurements of quality of life and presence of pain we have shown a clear negative impact of chronic abdominal pain six months after surgery on quality of life and functional status.

Our group previously reported a higher prevalence of, predominantly, infectious complications when adhesions were present in the abdominal cavity and had to be lysed to perform the intended procedure. The complication rate of postoperative pneumonia and wound infections more than doubled when an inadvertent enterotomy occurred.[17] In this large subgroup of the LAPAD cohort we have found comparable relationships between adhesiolysis and morbidity and readmissions, and now demonstrate that major complications and readmissions negatively impact quality of life and functional status at 6 months after surgery, albeit that adhesiolysis is not independently associated with reduced quality of life or functional status in our multi-variable regression analysis. A relationship between major complications and low postoperative quality of life has previously reported in a systematic review, however, results of this review should be interpreted with caution due to heterogeneity in quality of life questionnaires and in definitions of postoperative complications, missing baseline measurements and unclear duration of follow-up in some studies.[7] A short-term impact of complications and readmission on quality of life and physical functioning after surgery is plausible and a six months follow-up might be relatively short for complete physical and mental recovery. Shortly after a negative treatment experience patients value their quality of life lower, and assessment of quality of life and functional status may change following complications and readmission.[26, 27] A previous quality of life study with 2 years of follow-up, however, showed only marginal improvements after 6 months.[12] Interpreting this finding, higher quality of life results are not to be expected for our patients with a longer follow up. Notably, in both patients groups overall quality of life was not improved six months after surgery compared to before surgery and general health was even significantly lower. Lack of improvement in quality of life and functional performance after abdominal operations has important consequences for shared decision making, particularly in elderly patients who mostly focus on keeping or restoring their functional independence after surgery.[28]

Higher age and pulmonary morbidity were independent risk factor for reduced postoperative quality of life and functional performance. Due to small numbers we could not perform a separate analyses of elderly patients but they likely have a lower preoperative functional status, suffer from more postoperative complications and are

readmitted within 30 days more often.[29-31] Therefore it is not surprising that our study found a decreased quality of life and functional status for elderly patients. The indication for surgery did not seem to impact quality of life or functional status 6 months after surgery.

This is a large study assessing quality of life in a prospective cohort of patients undergoing elective abdominal surgery with pre- and postoperative quality of life and functional performance measurements, and detailed data of patients and procedures. Strengths are the large sample size and a completed follow-up of 78% which make the results generalizable for patients undergoing open elective abdominal surgery in a general surgery department of an academic hospital. Although heterogeneous, this reflects the mixed population in departments of general surgery and increases the generalizability of our results. Patients who did not respond to the questionnaire showed a trend towards a lower preoperative quality of life, which finding corresponds with earlier reports.[32] Thus, quality of life might have been overestimated in this study. Results should be extrapolated with caution regarding patients undergoing laparoscopic surgery because they are underrepresented in this study. A higher quality of life after laparoscopic surgery has been reported compared to open procedures.[33] The LAPAD cohort was studied between 2008 and 2010. Arguably, selection and perioperative management of patients might have changed after these years, although these are likely to be minimal because our hospital adopted 'enhanced recovery after surgery' programs as early as 2006.[34, 35] A range of different quality of life measurement instruments are available, we chose the DASI and SF-36 questionnaires because they measure both general functional status and quality of life. This corresponds with the aim of our study, to assess the impact of adhesiolysis on midterm general quality of life after general abdominal surgery.

Awareness of the impact of age, concomitant pulmonary disease and the possible occurrence of postoperative complications, readmissions and chronic abdominal pain on quality of life and functional status should lead to improved pre-operative counseling of patients. Especially, in case of benign and relative indications for surgery these factors are important to incorporate in shared-decision making because functional status and quality of life does not seem to improve postoperatively. Clinicians should meticulously query the presence of abdominal pain during pre- and postoperative consultations and take appropriate treatment measures. Additionally, programs to enhance pre-operative functional status might lead to improved postoperative functional status. Collecting quality of life and functional status after every medical and surgical treatment at multiple time points could lead to a more complete and transparent evaluation of quality of care and thus ultimately, lead to improved care.

Conclusion

Adhesiolysis in itself does not affect functional status and quality of life of patients six months after surgery. Major postoperative complications, readmissions, chronic abdominal pain, higher age and concomitant pulmonary disease have a negative impact on postoperative quality of life and the functional status. Higher preoperative quality of life and functional status is predictive for higher postoperative functional status and quality of life.

Supplement 1 Univariable ANCOVA analysis of postoperative SF-36 score corrected for baseline SF-36 score.

Patient factors	B	Standard error	95% Confidence interval		p
Sex					
Male	Ref.				
Female	- 0.16	0.18	- 0.05	0.02	0.38
Age	- 0.00	0.00	- 0.00	0.00	0.21
BMI	0.00	0.00	- 0.00	0.00	0.75
Smoking status					
Non-smoker	Ref.				
Ex-smoker	- 0.03	0.02	- 0.07	0.01	0.17
Smoker	- 0.03	0.03	- 0.08	0.02	0.26
P-Possum score	- 0.00	0.00	- 0.00	- 0.00	0.01
Comorbidity					
Pulmonary disease	- 0.09	0.03	- 0.15	- 0.03	<0.01
Diabetes	- 0.02	0.03	- 0.07	0.04	0.58
History of myocardial infarction	- 0.06	0.03	- 0.13	0.00	0.06
Renal failure	- 0.07	0.05	- 0.17	0.03	0.16
Pre-operative abdominal pain	- 0.01	0.02	- 0.05	0.03	0.68
Number of previous abdominal operations					
0	Ref.				
1 or 2	- 0.01	0.02	- 0.05	0.03	0.73
≥3	- 0.04	0.02	- 0.09	0.00	0.07
Presence of an ostomy before surgey	- 0.05	0.03	- 0.11	0.01	0.04
Indication for surgery					
Malignancy	- 0.02	0.02	- 0.05	0.02	0.41
Hernia	- 0.01	0.02	- 0.05	0.04	0.82
Other	0.02	0.02	- 0.02	0.06	0.33
Surgical approach					
Open	Ref.				
Laparoscopic	0.09	0.03	0.03	0.15	<0.01
Anatomical site of operation					
Lower gastrointestinal tract	0.03	0.02	- 0.00	0.07	0.06
Abdominal wall	0.01	0.02	- 0.04	0.05	0.73
Upper gastrointestinal tract	- 0.03	0.03	- 0.09	0.03	0.32
Hepatic-pancreatic-billiary	- 0.01	0.02	- 0.05	0.04	0.77
Other	- 0.05	0.03	- 0.11	0.00	0.05
Adhesiolysis time					
None	Ref.				
0 – 30 minutes	- 0.00	0.20	- 0.04	0.04	0.91
>30 minutes	- 0.04	0.02	- 0.08	0.01	0.14

Supplement 1 Continued.

Patient factors	B	Standard error	95% Confidence interval		p
Severity of adhesions underneath incision					
No, or mild adhesions	Ref.				
Severe adhesions	- 0.04	0.02	- 0.07	0.00	0.07
Severity of adhesions operative area					
No, or mild adhesions	Ref.				
Severe adhesions	- 0.02	0.02	- 0.06	0.02	0.26
Adhesiolysis related complications					
Enterotomy	- 0.00	0.04	- 0.08	0.07	0.95
Serosal injury	- 0.06	0.02	- 0.10	- 0.01	0.01
Other organ injury	-0.06	0.03	-0.01	0.13	0.09
Creation of an ostomy					
Colostomy	0.02	0.03	- 0.05	0.09	0.60
Ileostomy	- 0.00	0.03	- 0.06	0.05	0.93
Number of patients with complications					
Clavien-dindo grade 1	- 0.03	0.02	- 0.08	0.01	0.15
Clavien-dindo grade 2	- 0.05	0.02	- 0.09	- 0.01	0.02
Clavien-dindo grade 3	- 0.05	0.03	- 0.10	- 0.01	0.03
Clavien-dindo grade 4	- 0.18	0.05	- 0.29	- 0.08	<0.01
Readmissions during follow-up					
Readmission within 30 days	-0.09	0.03	-0.14	-0.04	<0.01
Readmission after 30 days	-0.07	0.03	-0.12	-0.02	<0.01
Chemotherapy during follow-up	- 0.01	0.03	- 0.06	0.04	0.77
Postoperative abdominal pain 6 months after surgery	- 0.13	0.02	- 0.17	- 0.10	<0.01
Preoperative SF-36 score	0.54	0.04	0.46	0.62	<0.01

Supplement 2 Univariable ANCOVA analysis for the postoperative DASI score, corrected for baseline DASI score.

Patient factors	B	Standard error	95% Confidence interval		p
Sex					
Male	Ref.				
Female	- 1.71	1.19	- 4.04	0.62	0.15
Age	- 0.22	0.04	- 0.30	- 0.13	<0.01
BMI	- 0.11	0.13	- 0.37	0.15	0.42
Smoking status					
Non-smoker	Ref.				
Ex-smoker	- 2.13	1.28	- 4.63	0.37	0.1
Smoker	- 3.93	1.69	- 7.26	- 0.61	0.02
P-Possum score	- 0.17	0.07	- 0.29	- 0.04	0.01
Comorbidity					
Pulmonary disease	- 7.58	1.95	- 11.42	- 3.74	<0.01
Diabetes	- 0.53	1.79	- 4.05	2.99	0.77
History of myocardial infarction	- 4.64	2.29	- 9.15	- 0.14	0.04
Renal failure	- 6.01	3.36	- 12.61	0.59	0.07
Pre-operative abdominal pain	- 0.15	1.27	- 2.64	2.34	0.90
Number of previous abdominal operations					
0	Ref.				
1 or 2	- 0.02	1.36	-2.65	2.65	0.99
≥3	- 1.17	1.58	- 4.26	1.93	0.46
Presence of an ostomy before surgey	- 2.39	1.95	- 6.21	1.44	0.22
Indication for surgery					
Malignancy	- 3.05	1.17	- 5.35	- 0.75	0.01
Hernia	1.76	1.52	- 1.22	4.74	0.25
Other	2.07	1.21	- 0.31	4.45	0.09
Surgical approach					
Open	Ref.				
Laparoscopic	5.42	2.08	1.34	9.50	0.01
Anatomical site of operation					
Lower gastrointestinal tract	1.31	1.18	- 1.00	3.62	0.26
Abdominal wall	1.31	1.54	- 1.71	4.33	0.40
Upper gastrointestinal tract	- 0.05	1.91	- 3.80	3.70	0.98
Hepatic-pancreatic-billiary	- 1.69	1.51	- 4.65	1.27	0.26
Other	- 2.45	1.81	- 6.01	1.11	0.18
Adhesiolysis time					
None	Ref.				
0 – 30 minutes	- 1.51	1.32	- 4.10	1.08	0.25
>30 minutes	- 1.51	1.59	- 4.63	1.60	0.34

Supplement 2 Continued.

Patient factors	B	Standard error	95% Confidence interval		p
Severity of adhesions underneath incision					
No, or mild adhesions	Ref.				
Severe adhesions	- 1.78	1.27	- 4.27	0.71	0.16
Severity of adhesions operative area					
No, or mild adhesions	Ref.				
Severe adhesions	- 0.68	1.28	- 3.20	1.84	0.60
Adhesiolysis related complications					
Enterotomy	- 0.89	2.53	- 5.87	4.08	0.73
Serosal injury	- 2.58	1.49	-5.50	0.34	0.08
Other organ injury	- 4.38	2.28	- 0.10	8.85	0.06
Creation of an ostomy					
Colostomy	- 0.63	2.28	- 5.12	3.85	0.78
Ileostomy	- 0.14	1.79	- 3.65	3.38	0.94
Postoperative complications					
Clavien-dindo grade 1	- 2.37	1.57	- 0.72	5.46	0.13
Clavien-dindo grade 2	- 4.19	1.39	- 6.92	- 1.47	<0.01
Clavien-dindo grade 3	- 4.36	1.64	- 7.58	- 1.13	0.01
Clavien-dindo grade 4	- 9.73	3.89	- 16.78	- 2.69	0.01
Readmissions during follow-up					
Readmission within 30 days	- 6.14	1.66	- 9.41	- 2.87	<0.01
Readmission after 30 days	- 6.04	1.62	- 9.22	- 2.86	<0.01
Chemotherapy during follow-up	- 0.19	1.61	- 3.34	2.97	0.91
Postoperative abdominal pain 6 months after surgery	- 4.98	1.20	- 7.34	- 2.62	<0.01
Preoperative DASI score	0.61	0.03	0.54	0.67	<0.01

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Chapter 5

Risk of pain and gastrointestinal complaints after elective abdominal surgery

Chema Strik, M.D.; Barend van den Beukel, M.D.; Dagmar van Rijckevorsel, M.D.;
Martijn W.J. Stommel, M.D., PhD; Richard P.G. ten Broek, M.D., PhD;
Harry van Goor, M.D., PhD, FRCS
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
Submitted

Abstract

Objectives: The incidence of chronic postoperative abdominal pain (CPAP) after abdominal surgery is substantial and decreases overall quality of life. One in three patients report to have pain-related interference with mood, sleep and enjoyment of life and 12% visit the emergency department for pain related symptoms. Previous studies lack data on preoperative health and pain status, or are limited by small patient samples. The aim of this study is to assess risk factors for CPAP and gastrointestinal complaints.

Methods: Prospective cohort study including patients undergoing an elective laparotomy or laparoscopy at a tertiary referral centre. Relevant patient, pain, surgical, and medical data as well as the Gastrointestinal Symptom Rating Scale (GSRS) were assessed before, during and after hospital stay and at the outpatient clinic until 6 months after discharge. Linear and logistic regression analysis were used to assess risk factors.

Results: Out of 518 included patients, 184 (36%) had CPAP. The median GSRS score was 5 (IQR 3 – 10). The presence of pre-operative pain shorter (OR 2.69; p 0.016) or longer than three months (OR 3.99; p 0.000), usage of opioid analgesia preoperatively (OR 3.54; p 0.001), severe adhesions underneath the incision (OR 1.63; p 0.040) and the NRS pain score on postoperative day 2 (OR 1.23; p 0.004) showed to independently increase the risk for chronic abdominal pain. Chronic pancreatitis as indication for surgery (B 4.20; p 0.03), 3 or more previous abdominal operations (B 1.03; p 0.03), presence of pain more than 3 months before surgery (B 1.61; p <0.01), upper gastrointestinal tract as the anatomical location of surgery (B 1.43; p 0.03) and a higher preoperative GSRS score (B 0.36; p <0.01) independently increased the GSRS score six months after surgery.

Discussion: The duration and severity of preoperative pain, more severe acute postoperative pain and the presence of anxious and depressive symptoms were the most relevant risk factors for CPAP. The number of operations and the anatomical location of the operation showed to be important risk factors for increasing the number of gastrointestinal complaints.

Introduction

The incidence of chronic postoperative abdominal pain (CPAP) is estimated at 11% after abdominal surgery. CPAP is associated with an increase of gastrointestinal symptoms and decreases overall quality of life.[1, 2] Around 30% patients after gastrointestinal surgery report to have pain-related interference with mood, sleep and enjoyment of life and 12% visit the emergency department for pain related symptoms.[3] Intra-abdominal adhesions are deemed as the cause of CPAP in 60% of the patients. In these patients no anatomic or functional abnormalities are found apart from adhesions. [4] Adhesions are linked to several gastrointestinal complaints such as bloating and irregular bowel habits.[5] Causality between adhesions, chronic pain and abdominal symptoms is disputed, mainly due to doubt regarding the long term efficacy of surgical adhesiolysis as treatment of pain.[6, 7]

Most studies regarding chronic post-surgical pain are performed in patients undergoing other types than abdominal surgery and report various risk factors including demographic, perioperative and psychological factors.[8, 9] The few studies that have been performed in abdominal surgery show an increased risk for female gender, lower age, preoperative anxiety and depression in developing CPAP. However, studies lack data on preoperative health and pain status, or are limited by small patient samples.[1, 3] Generalizability of these results is also limited due to a lack of standardization of outcome measures.[10]

In a large prospective database pain-related measurements and a questionnaire regarding gastro-intestinal complaints have been collected before and after abdominal surgery. [11] Combined with a comprehensive assessment of baseline and peri-operative data, this database provides a unique opportunity to study pre- and postoperative pain and gastrointestinal symptoms and to relate these with baseline adhesions and adhesiolysis data.

The aim of this study is to assess risk factors for CPAP and gastrointestinal complaints in a large prospective cohort of patients who undergo primary and repeat elective abdominal surgery.

Methods

Study design and patients

This study is part of the LAPAD (LAParotomy or LAParoscopy and ADhesiolysis) study (clinicaltrials.gov registration number: NCT01236625). In the LAPAD study adult patients undergoing an elective laparotomy or laparoscopy at the department of surgery of the Radboud university medical center between June 2008 and June 2010 were included. Patients younger than 18 years or patients with a mental disorder were excluded. The LAPAD study was approved by the local medical ethical committee and detailed methods were published.[11] Relevant patient, surgical, and medical data were prospectively assessed before, during and after hospital stay and at the

outpatient clinic until 6 months after discharge. One predefined objective of the LAPAD study was to establish the relation between adhesions and adhesiolysis and pre- and postoperative pain and gastrointestinal complaints.
Patients who participated in the LAPAD study completed the Gastrointestinal Symptom Rating Scale (GSRS) and the Short Form (SF-36) the day before undergoing surgery. Six months after discharge the GSRS and a questionnaire regarding any readmissions was sent to patients. Additionally, data regarding new admissions was collected from medical records of hospitals, general practitioners and nursing homes when applicable. Patients who underwent a second elective abdominal operation that was included in the LAPAD study were not asked to fill in a questionnaire before their second operation. Patients who did not complete the pre- and postoperative GSRS questionnaires were excluded.

Variables

The severity of pain was determined with a numeric rating scale (NRS) and was categorized as no pain, a NRS of less than 4 or a NRS of 4 or greater. The duration of preoperative pain was classified as no pain, pain existing for 3 months or less, pain existing longer than 3 months. Usage of analgesia was categorized as no usage of analgesia, NSAID or acetaminophen only or usage of opioid analgesia.
The GSRS is a questionnaire that measures the impact of gastrointestinal complaints on overall functioning. A higher score correlates to more impaired functioning.[12]
The SF-36 measures overall quality of life and was used to measure the preoperative mental and emotional health of patients.[13]
Baseline demographics included sex, age, body mass index, smoking status, preoperative mental health, role emotional, social functioning and vitality subscales of the SF-36 and the number of previous abdominal operations (none, 1 or 2 or ≥3). The indication for the operation was categorized as malignancy, ventral hernia, ulcerative colitis, Crohn's disease, chronic pancreatitis, diverticulitis or other reasons.
Characteristics of the planned operation included surgical approach (median, sub-costal or other incision, and laparoscopic procedures), anatomical site of the operation (upper gastrointestinal tract, lower gastrointestinal tract, hepatobiliary-pancreatic, abdominal wall, or other), the duration of surgery in minutes and the presence of adhesions. The severity of adhesions underneath the previous incision and at the operative area were assessed using the Zühlke classification, comprising grade 0, 1 and 2 as no or mild adhesions and grade 3 and 4 as severe adhesions. Adhesiolysis time was measured in minutes from the start of adhesiolysis until the operative area was cleared of adhesions.
The incidence of any intra-abdominal complications within 30 days of the index operation, comprising intra-abdominal sepsis, abscess, anastomotic leakage, fistula, delayed diagnosed perforation and postoperative hemorrhage were collected after

the operation. Epidural analgesia was noted. Acute postoperative pain was registered using the NRS, with a minimal and a maximal value for each postoperative day until day 5.
The endpoints of this study were the presence of abdominal pain six months post-operatively (chronic abdominal pain) and the total postoperative GSRS score. The presence of abdominal pain was extracted from the GSRS questionnaire and was defined as no abdominal pain or abdominal pain interfering with social activities.

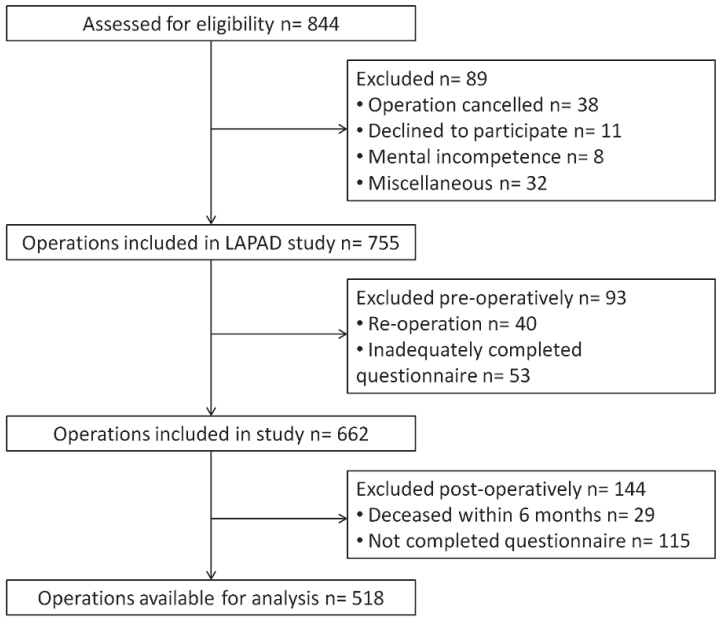
Statistical methods

Continuous variables are presented as means with standard deviation, or medians with interquartile range if non-normal distribution. Dichotomous or categorical variables are presented as absolute numbers and percentages.
Due to missing data of the acute postoperative NRS score, we performed a multiple imputation with predictive mean matching analysis for the minimal and maximal NRS values of postoperative day 0, 1, 2, 3, 4 and 5 using all baseline characteristics and the presence of postoperative abdominal pain for prediction. All values were imputed 20 times and the pooled OR, 95 per cent confidence interval and p-values were used for the univariable and multivariable logistic regression. The minimal and maximal NRS values of postoperative day 2 were used in the analysis because this was the last postoperative day on which more than 95% of the patients were still admitted to the surgical ward.
A univariable logistic regression analysis was used to assess risk factors for chronic abdominal pain and a univariable linear regression was performed for risk factors for the total postoperative GSRS score. All variables in the univariable analysis with a $p < 0.10$ were considered for their respective multivariable analysis. For both the multivariable logistic and linear regression analyses, a stepwise, backwards selection procedure was used with a P entry ≤0.10 and P stay ≤0.10. For the linear regression analysis the regression coefficient (B) is presented with a 95% CI, for the logistic regression analysis the Odds Ratio (OR) and 95% CI were calculated. If significant co-linearity was detected, the multivariable analysis was repeated with and without the variables causing co-linearity.
A value of $p \leq 0.05$ was considered significant. Statistical analysis was performed using SPSS for Windows version 20.0 software (SPSS, Chicago, IL). We excluded per analysis the cases with missing data.

Results

755 operations included in the LAPAD study were assessed for eligibility in this study. 93 operations were not included due to incomplete questionnaires (53) or because the same patient was operated multiple times during the LAPAD study(40). 662 patients were included in the study, 29 patients deceased within 6 months and 115 patients did not return the questionnaires 6 months postoperatively. Thus, 518 (78%) patients were available for analysis (figure 1). Six (1%), ten (2%) and twelve (2%) patients had missing data regarding the severity of adhesions underneath the incision, operative area and other areas respectively. 188 (35%) patients had missing data on the post-operative NRS score at day 2.

Figure 1 Flow-chart.



Baseline characteristics

The baseline characteristics are shown in table 1. The indication for surgery was a malignancy in 47%, a ventral hernia in 19% or other indications in 27%. The anatomical location of surgery was the lower gastrointestinal tract in 221 (43%), the hepato-biliary-pancreatic tract in 94 (18%) and the abdominal wall in 90 (17%) patients.

A median incision was used in 343 (66%) patients and 159 (31%) patients had severe adhesions underneath the incision. Pre-operatively, 165 (33%) patients had abdominal pain of whom 129 (26%) patients reported a NRS score of 4 or higher. 412 (80%) patients did not use analgesia, whereas 48 (9%) used opioid analgesia pre-operatively. 144 (28%) patients had abdominal pain more than 3 months before surgery. The median score of the GSRS before the operation was 6 (IQR 3 – 10). Postoperatively, the median minimal value of the NRS was 2 (0 – 4) and the median maximal value was 4 (2 – 5). 49 (10%) patients developed an intra-abdominal complication.

Table 1 Baseline characteristics; † mean and standard deviation, all other values are percentiles or median with interquartile range.

Patient factors	Included patients (N = 518)
Sex	
Male	296 (57%)
Female	222 (43%)
Age†	58 (± 13)
BMI†	25.86 (± 4.40)
P-Possum score	2.25 (0.90 – 5.80)
Preoperative Mental Health subscale SF-36	0.72 (0.60 – 0.88)
Preoperative Role Emotional subscale SF-36	1.00 (0.33 – 1.00)
Preoperative Social Functioning SF-36	0.75 (0.50 – 1.00)
Preoperative Vitality subscale SF-36	0.60 (0.40 – 0.80)
Number of previous abdominal operations	
0	181 (35%)
1 or 2	212 (41%)
≥3	125 (24%)
Indication for surgery	
Malignancy	242 (47%)
Ventral Hernia	96 (19%)
Ulcerative colitis	10 (2%)
Crohn's disease	14 (3%)
Chronic pancreatitis	10 (2%)
Diverticulitis	12 (2%)
Other	141 (27%)
Pre-operative abdominal pain and gastrointestinal complaints	
Severity of preoperative pain	
No pain	339 (67%)
NRS ≥1 and <4	36 (7%)
NRS ≥4	129 (26%)

Table 1 Continued.

Patient factors	Included patients (N = 518)
Presence of pain in time	
No pain	339 (65%)
Pain ≤ 3 months	35 (7%)
> 3 months	144 (28%)
Usage of analgesia	
No analgesia	412 (80%)
Only NSAID or Acetominophen	58 (11%)
Opioid analgesia	48 (9%)
Preoperative GSRS score	6 (3 – 10)
Surgical factors	
Anatomical location of surgery	
Upper gastrointestinal tract	53 (10%)
Lower gastrointestinal tract	221 (43%)
Hepato-billiary-pancreatic	94 (18%)
Abdominal wall	90 (17%)
Other	60 (12%)
Surgical approach	
Median incision	343 (66%)
Subcostal incision	76 (15%)
Other	55 (10%)
Laparoscopy	44 (9%)
Severity of adhesions underneath incision	
No, or mild adhesions	353 (69%)
Severe adhesions	159 (31%)
Severity of adhesions at operation area	
No, or mild adhesions	354 (70%)
Severe adhesions	144 (30%)
Severity of adhesions at other abdominal areas	
No, or mild adhesions	407 (80%)
Severe adhesions	99 (20%)
Duration of adhesiolysis (minutes)	5 (0 – 26)
Duration of surgery (minutes)	205 (146 – 271)
Creation of an ostomy	
Colostomy	36 (7%)
Ileostomy	63 (12%)
Acute postoperative pain	
Epidural analgesia	284 (55%)
NRS day 2	
Minimal value	2 (0 – 4)
Maximal value	4 (2 – 5)
Postoperative complications	
Intra-abdominal complication	49 (10%)
Relaparotomy	53 (10%)

The characteristics of the non-responders are shown in table 2. Compared to responders, non-responders had more often a preoperative NRS >4 (p = 0.01), abdominal pain for longer than 3 months (p = 0.01) and preoperative opioid analgesia use (p = 0.04). They had a lower preoperative vitality score on the subscale (p = <0.01) and tended to have a lower preoperative mental health score on the subscale (p = 0.09) of the SF-36 questionnaire.

Table 2 Characteristics of patients who did not return the questionnaire six months after discharge; † mean and standard deviation, all other values are percentiles or median with interquartile range.

	Patients who returned the GSRS (n= 518)	Patients who did not return the GSRS (n= 115)	p-value
Sex			0.42
Male	296 (57%)	61 (53%)	
Female	222 (43%)	54 (47%)	
Age†	58 (± 13)	55 (± 17)	0.04
BMI†	25.86 (± 4.40)	25.29 (± 4.36)	0.21
Preoperative Mental Health subscale SF-36	0.72 (0.60 – 0.88)	0.68 (0.60 – 0.80)	0.09
Preoperative Role Emotional subscale SF-36	1.00 (0.33 – 1.00)	1.00 (0 – 1.00)	0.84
Preoperative Social Functioning SF-36	0.75 (0.50 – 1.00)	0.75 (0.50 – 1.00)	0.39
Preoperative Vitality subscale SF-36	0.60 (0.40 – 0.80)	0.50 (0.30 – 0.70)	<0.01
Number of previous abdominal operations			0.73
0	181 (35%)	37 (32%)	
1 or 2	212 (41%)	53 (46%)	
≥3	125 (24%)	25 (22%)	
Preoperative GIC score	6 (3 – 10)	8 (4 – 12)	0.04
Indication for surgery			
Malignancy	242 (47%)	48 (42%)	0.33
Surgical approach			0.18
Median incision	343 (66%)	72 (63%)	
Subcostal incision	76 (15%)	13 (11%)	
Other	55 (11%)	13 (11%)	
Laparoscopy	44 (8%)	17 (15%)	
Preoperative abdominal pain			0.01
No pain	339 (67%)	58 (52%)	
NRS <4	36 (7%)	13 (11%)	
NRS >4	129 (26%)	41 (37%)	
Presence of pain in time			0.01
No pain	339 (67%)	58 (52%)	
Pain ≤ 3 months	35 (7%)	15 (13%)	
> 3 months	144 (28%)	42 (37%)	

Table 2 Continued.

	Patients who returned the GSRS (n= 518)	Patients who did not return the GSRS (n= 115)	p-value
Usage of analgesia			0.04
No analgesiaNSAID	412 (80%)	82 (71%)	
Only NSAID or Acetominophen	58 (11%)	13 (11%)	
Opioid analgesia	48 (9%)	20 (17%)	
NRS day 2			
Minimal value	2 (0 – 4)	2 (0 – 4)	0.97
Maximal value	4 (2 – 5)	3 (2 – 5)	0.82

Abdominal pain and complaints 6 months after surgery

Six months after surgery, 184 (36%) patients had abdominal pain impairing social functioning. The median GSRS score was 5 (IQR 3 – 10) (table 3). The most commonly reported symptoms were borborygmus by 310 (60%) patients, abdominal distension by 242 (57%), eructation by 260 (50%) patients and increased flatulence by 339 (65%) patients. 123 (24%) patients reported to have fecal incontinence impacting social functioning. Only 33 patients (6%) had no gastrointestinal complaints six months after surgery.

Table 3 Abdominal pain and gastrointestinal complaints six months after surgery; all values are percentiles, except the postoperative GSRS score which is represented with a median value with interquartile range.

	Included patients (N=518)
Intra-abdominal pain interfering with social functioning 6 months after surgery	184 (36%)
Postoperative GSRS score	5 (3 – 10)
Heartburn	138 (27%)
Acid regurgitation	129 (25%)
Sucking sensations in the epigastrium	129 (25%)
Nausea and vomiting	155 (30%)
Borborygmus	310 (60%)
Abdominal distension	242 (57%)
Eructation	260 (50%)
Increased flatus	339 (65%)
Obstipation	60 (12%)
Diarrhea	88 (17%)
Fecal incontinence	123 (24%)

Risk factors for abdominal pain six months after surgery

The univariable analysis showed that female gender, number of previous abdominal operations, chronic pancreatitis and other indications for surgery, a preoperative NRS ≥4, pain existing longer than 3 months before surgery, usage of opioids as analgesic before surgery, other incisions, duration of adhesiolysis and of operation, severe adhesions underneath the incision and a higher NRS score at postoperative day 2 all significantly increased the risk for the presence of abdominal pain six month after surgery. A higher age, higher BMI, preoperative mental health, role emotional, social functioning and vitality SF-36 subscores, malignancy as indication for surgery, no pain before surgery and no usage of analgesia significantly decreased the risk for having abdominal pain six months after surgery (supplement 1).

In the multivariable analysis, co-linearity was detected between the number of previous laparotomies and the presence of adhesions. After repeating the multivariable analysis, both variables were removed due to an increase in their respective p-values. The presence of pain either shorter (OR 2.69; p 0.016) or longer than three months (OR 3.99; p 0.000), usage of opioid analgesia preoperatively (OR 3.54; p 0.001), severe adhesions underneath the incision (OR 1.63; p 0.040) and a higher minimal NRS value on postoperative day 2 (OR 1.23; p 0.004) showed to independently increase the risk for chronic abdominal pain. Factors independently decreasing the risk for having abdominal pain six months after surgery were higher age (OR 0.97; p 0.001), BMI (OR 0.93; p 0.006), preoperative mental health (OR 0.32; p 0.045), and usage of a median incision (OR 0.52; p 0.006) (table 4).

Risk factors for gastrointestinal complaints

In the univariable analysis, the number of previous operations, chronic pancreatitis as indication for surgery, a preoperative NRS ≥4, presence of pain longer than 3 months before surgery, usage of opioid analgesia preoperatively, severe adhesions not in the operative area and a higher preoperative GSRS score significantly increased the postoperative GSRS score. Malignancy and ulcerative colitis as indication for surgery, no preoperative pain, no preoperative usage of analgesia and creation of a colostomy decreased the postoperative GSRS score (supplement 2).

Chronic pancreatitis as indication for surgery (B 4.20; p 0.03), 3 or more previous abdominal operations (B 1.03; p 0.03), presence of pain more than 3 months before surgery (B 1.61; p <0.01), upper gastrointestinal tract as the anatomical location of surgery (B 1.43; p 0.03) and a higher preoperative GSRS score (B 0.36; p <0.01) independently increased the GSRS score six months after surgery. Higher preoperative mental health score (B – 2.10; p 0.04), ulcerative colitis as indication for surgery (B – 5.58; p <0.01) and creation of a colostomy at the end of surgery (B – 2.11; p 0.01) independently decreased the postoperative GSRS score six months after surgery (table 5).

Table 4 Multivariable logistic regression analysis for having chronic postoperative abdominal pain.

Patient factor	OR	95% CI OR		p
Age†	0.97	0.96	0.99	0.001
BMI†	0.93	0.89	0.98	0.004
Preoperative Mental Health subscale SF-36	0.32	0.11	0.98	0.045
Presence of pain in time				
No pain	Ref.			
Pain ≤ 3 months	2.69	1.21	6.00	0.016
> 3 months	3.99	2.48	6.42	0.000
Usage of analgesia				
Opioid analgesia	3.54	1.66	7.57	0.001
Surgical approach				
Median incision	0.52	0.33	0.83	0.006
Anatomical location of surgery				
Upper gastrointestinal tract	1.85	0.91	3.77	0.091
Creation of a colostomy	0.40	0.15	1.05	0.064
Severe adhesions underneath incision	1.63	1.02	2.59	0.011
NRS day 2				
Minimal value	1.23	1.07	1.41	0.004

Table 5 Multivariable logistic regression analysis for having gastrointestinal complaints six months after surgery.

Patient factor	B	95% CI B		p
Age†	- 0.02	- 0.06	0.00	0.07
Preoperative Mental Health subscale SF-36	- 2.10	- 4.07	- 0.13	0.04
Indication for surgery				
Ulcerative colitis	- 5.58	- 8.39	- 2.77	<0.01
Chronic pancreatitis	4.20	1.41	6.99	<0.01
Number of previous abdominal operations				
≥3	1.03	0.10	1.96	0.03
Presence of pain in time				
> 3 months	1.61	0.58	2.65	<0.01
Anatomical location of surgery				
Upper gastrointestinal tract	1.43	0.15	2.72	0.03
Creation of a colostomy	- 2.11	- 3.62	- 0.61	0.01
Preoperative GSRS score	0.36	0.28	0.44	<0.01

Discussion

Over one third of the patients reported having chronic postoperative pain impacting social functioning and almost every patient had gastro-intestinal symptoms at six months after elective abdominal surgery. Preoperative pain, preoperative usage of opioid analgesia and more severe pain in the acute postoperative phase were the most relevant risk factors for chronic postoperative pain. Only severe adhesions underneath a midline incision were associated with chronic postoperative pain, further adhesion and adhesiolysis related parameters did not show importance for chronic pain. Chronic pancreatitis as indication for surgery , upper GI surgery and preoperative pain were the most relevant risk factors for postoperative gastro-intestinal symptoms. The few studies on abdominal surgical procedures show comparable incidences for CPAP, ranging between 18 to 32 percent.[1, 14] Gastrointestinal, hernia, breast and thoracic operations share similar risk factors for developing chronic postoperative pain such as female gender, younger age, and most importantly preexisting pain and low mental health status.[15] A minimal invasive approach does not seem to decrease the occurrence of postoperative chronic pain.[16] Long term preexisting pain, pre-operative opioid usage and more severe acute postoperative pain were the most relevant risk factors for CPAP. In contrast to some reports our data collection regarding preoperative factors was prospective and comprehensive and our analysis was rigorous, taking into account potential bias of missing and non-responders data. In addition to a large sample size and an almost 80 percent complete follow up, results are robust and generalizable to patients who undergo elective abdominal surgery.[17] A lower preoperative score on the mental health subscale increased the risk for CPAP and gastrointestinal complaints. The mental health subscale measures nervousness and depressive symptoms in patients.[13] Both psychological variables increase the risk for severe acute and chronic postoperative pain and more healthcare utilization.[3, 18] Altogether this suggests that patient and pain-related factors rather than surgical factors determine chronic postoperative pain. Outcomes are probably an under-estimate because risk factors were more frequent in non-responders.

The association between adhesion (re)formation and chronic postoperative pain and gastrointestinal symptoms is subject of debate. Adhesion reformation after adhesiolysis is a more aggressive process with dense fibrous tissue formation which theoretically might result in chronic pain.[19, 20] At baseline, patients with adhesions had more often preoperative pain (results not shown). We found that more severe adhesions under-neath the incision significantly increased the risk for postoperative abdominal pain. More severe adhesions underneath the incision are a reflection of the number of previous laparotomies performed due to new or recurrent illness and conceivably preoperative pain.[21, 22] Adhesiolysis might also indirectly be responsible for CPAP through an increase in adhesiolysis related complications such as inadvertent enterotomy and intraabdominal abscess. Surgical complications, however, were not

identified as risk factor for chronic abdominal pain, possibly due to the low complication rate. A median incision showed to decrease the risk for having abdominal pain after surgery. In patients undergoing a hysterectomy usage of a pfannenstiel incision increased the risk for having pain after surgery.[23] A possible explanation might be that when the skin and muscle is transected transversely e.g. transverse and subcostal incision, more nerve tissue is injured.

Ninety percent of patients had any kind of gastrointestinal complaint six months after surgery and patients noted to have almost two times more often borborygmus, abdominal distension, eructation and increased flatulence impacting social functioning in comparison to abdominal pain. Our results indicate that the presence of pain, the number of operations and the location of the operation showed to be important risk factors for increasing the number of gastrointestinal complaints six months after surgery. Anatomical and physiological changes of the gastrointestinal tract after bowel resection and type of reconstruction may explain the higher prevalence of gastrointestinal complaints, for example, fecal incontinence in one quarter of patients and the lower GSRS score when reconstruction was not performed and an enterostomy was created.

Proper counseling and shared-decision making is important in treating patients and they should be aware that abdominal pain and gastrointestinal complaints may not decline after surgery. Surgeons should be aware of the high incidence of chronic postoperative pain and pay appropriate attention to the presence of pre-operative pain and psychological risk factors in the preoperative work up. Early involvement and postoperative follow-up of an anesthesiologist or pain specialist can improve direct postoperative pain management and limited evidence suggests that perioperative analgesia may result in a reduced incidence of chronic postoperative pain.[24, 25]

Conclusion

One in three patients will have chronic postoperative abdominal pain six months after elective abdominal surgery and 9 out of 10 patients gastrointestinal complaints. The duration and severity of preoperative pain, more severe acute postoperative pain and the presence of anxious and depressive symptoms were the most relevant risk factors whereas adhesions and adhesiolysis related problems were not evident as risk factor for CPAP. The number of operations and the anatomical location of the operation showed to be important risk factors for increasing the number of gastrointestinal complaints.

Supplement 1 Univariable logistic regression analysis for having chronic postoperative abdominal pain.

Patient factor	OR	95% CI OR		p
Pre-operative clinical factors				
Sex				
Male	Ref.			
Female	1.86	1.30	2.68	<0.01
Age	0.97	0.95	0.98	<0.01
BMI	0.95	0.91	0.99	0.01
Preoperative Mental Health subscale SF-36	0.16	0.06	0.41	<0.01
Preoperative Role Emotional subscale SF-36	0.62	0.41	0.93	0.02
Preoperative Social Functioning SF-36	0.29	0.16	0.53	<0.01
Preoperative Vitality subscale SF-36	0.17	0.08	0.35	<0.01
Number of previous abdominal operations				
0	Ref			
1 or 2	1.51	0.99	2.32	0.06
≥3	194	1.20	3.13	0.01
Indication for surgery				
Malignancy	0.47	0.32	0.68	<0.01
Ventral Hernia	1.05	0.66	1.67	0.83
Ulcerative colitis	0.20	0.03	1.57	0.13
Crohn's disease	2.49	0.85	7.28	0.10
Chronic pancreatitis	17.13	2.15	136.27	0.01
Diverticulitis	1.84	0.59	5.80	0.30
Other	1.71	1.15	2.54	0.01
Pre-operative abdominal pain assessment				
Severity of preoperative pain				
No pain	0.21	0.15	0.32	<0.01
NRS >0 and <4	1.66	0.90	3.08	0.11
NRS ≥4	4.89	3.21	7.43	<0.01
Presence of pain in time				
No pain	0.21	0.15	0.32	<0.01
Pain ≤ 3 months	1.58	0.79	3.15	0.20
> 3 months	4.75	3.16	7.15	<0.01
Usage of analgesia				
No analgesia	0.30	0.19	0.46	<0.01
Only NSAID or Acetominophen	1.68	0.97	2.92	0.07
Opioid analgesia	5.80	2.98	11.29	<0.01

Supplement 1 Continued.

Patient factor	OR	95% CI OR		p
Surgical factors				
Anatomical location of surgery				
Upper gastrointestinal tract	0.93	0.51	1.69	0.80
Lower gastrointestinal tract	1.09	0.76	1.57	0.64
Hepato-billiary-pancreatic	0.92	0.58	1.48	0.74
Abdominal wall	1.19	0.75	1.90	0.46
Other	0.75	0.42	1.35	0.34
Surgical approach				
Median incision	0.69	0.48	1.01	0.06
Subcostal incision	1.00	0.60	1.66	0.99
Other	2.04	1.16	3.58	0.01
Laparoscopy	1.16	0.61	2.19	0.65
Presence of adhesions	1.07	0.74	1.54	0.73
Severe adhesions underneath incision	1.57	1.07	2.30	0.02
Severe adhesions at operation area	1.37	0.93	2.02	0.12
Severe adhesions at other abdominal areas	1.28	0.82	2.01	0.28
Duration of adhesiolysis (minutes)	1.01	1.00	1.01	0.07
Duration of surgery (minutes)	1.00	1.00	1.00	0.07
Creation of an ostomy				
Colostomy	0.42	0.18	0.97	0.04
Ileostomy	1.23	0.71	2.10	0.46
Postoperative factors				
Epidural analgesia	0.79	0.55	1.14	0.21
NRS day 2				
Minimal value	1.30	1.16	1.46	<0.01
Maximal value	1.19	1.09	1.31	<0.01
Any intra-abdominal complication	0.87	0.46	1.63	0.66
Relaparotomy	0.69	0.37	1.29	0.25

Supplement 2 Univariable logistic regression analysis for having gastrointestinal complaints six months after surgery.

Pre-operative clinical factors	B	95% CI B		p
Sex				
Male	Ref.			
Female	0.21	- 0.61	1.03	0.61
Age†	- 0.03	- 0.06	0.00	0.06
BMI†	- 0.05	- 0.14	0.04	0.31
Preoperative Mental Health subscale SF-36	- 1.79	- 3.85	0.28	0.09
Preoperative Role Emotional subscale SF-36	- 0.56	- 1.21	0.70	0.60
Preoperative Social Functioning SF-36	- 0.25	- 1.67	1.18	0.74
Preoperative Vitality subscale SF-36	- 1.58	- 3.27	0.12	0.07
Number of previous abdominal operations				
0	Ref			
1 or 2	0.69	- 0.22	1.61	0.14
≥3	1.51	0.45	2.57	0.01
Indication for surgery				
Malignancy	- 0.84	- 1.66	- 0.03	0.04
Ventral Hernia	0.44	- 0.58	1.47	0.40
Ulcerative colitis	- 5.28	- 8.18	- 2.38	<0.01
Crohn's disease	0.17	- 2.32	2.66	0.89
Chronic pancreatitis	4.81	1.92	7.70	<0.01
Diverticulitis	1.89	- 0.76	4.55	0.16
Other	0.48	- 0.42	1.38	0.30
Pre-operative abdominal pain assessment				
Severity of preoperative pain				
No pain	- 1.54	- 2.52	- 0.57	<0.01
NRS >0 and <4	1.01	- 0.43	2.44	0.17
NRS ≥4	1.16	0.15	2.18	0.03
Presence of pain in time				
No pain	- 1.54	- 2.52	- 0.57	<0.01
Pain ≤ 3 months	- 0.44	- 2.03	1.15	0.59
> 3 months	1.95	0.91	2.99	<0.01
Usage of analgesia				
No analgesia	- 1.02	- 2.04	- 0.01	0.05
Only NSAID or Acetominophen	0.28	- 0.99	1.55	0.67
Opioid analgesia	1.61	0.21	3.01	0.03

Supplement 2 Continued.

Pre-operative clinical factors	B	95% CI B		p
Surgical factors				
Type of surgery				
Upper gastrointestinal tract	1.04	- 0.28	2.35	0.12
Lower gastrointestinal tract	- 0.74	- 1.56	0.08	0.08
Hepato-billiary-pancreatic	0.26	- 0.78	1.30	0.63
Abdominal wall	0.38	- 0.67	1.43	0.48
Other	- 0.12	- 1.37	1.14	0.86
Surgical approach				
Median incision	0.32	- 0.53	1.16	0.46
Subcostal incision	- 0.12	- 1.26	1.01	0.83
Other	0.31	- 0.99	1.60	0.64
Laparoscopy	- 1.09	- 2.53	0.34	0.14
Presence of adhesions	0.52	- 0.31	1.35	0.22
Severe adhesions underneath incision	0.51	- 0.37	1.38	0.26
Severe adhesions at operation area	0.19	- 0.70	1.08	0.67
Severe adhesions at other abdominal areas	1.17	0.15	2.20	0.03
Duration of adhesiolysis (minutes)	0.01	- 0.00	0.03	0.08
Duration of surgery (minutes)	- 0.00	- 0.01	0.00	0.26
Creation of an ostomy				
Colostomy	- 2.32	- 3.88	- 0.76	<0.01
Ileostomy	- 1.04	- 2.27	0.18	0.10
Postoperative factors				
Epidural analgesia	- 0.36	- 1.17	0.45	0.38
NRS day 2				
Minimal value	0.21	- 0.02	0.44	0.08
Maximal value	0.17	- 0.02	0.36	0.08
Any intra-abdominal complication	- 0.71	- 2.07	0.65	0.31
Relaparotomy	- 0.92	- 2.23	0.40	0.17
Preoperative GSRS	0.44	0.37	0.51	<0.01

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Chapter 6

Adhesiolysis in patients undergoing a repeat median laparotomy

Chema Strik, M.D., Martijn W.J. Stommel, M.D., PhD, Richard P.G. ten Broek, M.D.,
Prof. Harry van Goor, M.D., PhD, FRCS
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
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Abstract

Background: Adhesiolysis during repeat surgery is associated with a high incidence of iatrogenic enterotomies and an increase in postoperative complications. Identification of risk factors would improve preoperative counseling and operating room strategy.
Objective: The aim of this study was to identify pre-operative risk factors for prolonged and difficult adhesiolysis in a repeat median laparotomy.
Design: Prospective cohort study. Univariate and multivariate analyses were used to assess risk factors for prolonged and difficult adhesiolysis.
Settings: Radboud University Medical Center
Patients: Patients participating in the LAPAD study (clinicaltrials.gov NCT01236625) undergoing an elective repeat median laparotomy.
Main outcome measures: Detailed data regarding adhesiolysis to gain entry to the abdomen and adhesions underneath the previous incision were gathered by direct observation.
Results: A total of 259 patients underwent a repeat median laparotomy. Adhesiolysis was required for 230 patients (89%); the remaining 29 patients (11%) did not have adhesions underneath the incision. Median adhesiolysis time underneath the midline incision was 10 minutes (IQR: 5 – 25). 76 patients (29%) had grade 1 or grade 2 adhesions; 108 (42%) grade 3; and 46 (18%) grade 4. The number of previous laparotomies was the only independent risk factor for prolonged (p= ≤0.01; CI: 2.5 – 14.10) and difficult adhesiolysis (p= ≤0.01, OR 4.21 CI 1.74 – 10.17). History of peritonitis, anatomical location of previous surgery, and the time interval between consecutive median laparotomies did not prolong adhesiolysis.
Limitations: Retrospective data collection of patients' medical histories, no data on severity of previous peritonitis.
Conclusions: This study demonstrates that four or more previous laparotomies and the presence or history of an intra-peritoneal synthetic mesh are independently associated with a longer duration of adhesiolysis needed to gain access to the abdomen. A short time interval between median laparotomies or a history of peritonitis did not prolong the duration of adhesiolysis.

Introduction

Peritoneal adhesions develop in more than 90% of patients who have undergone abdominopelvic surgery.[1, 2] Complications due to peritoneal adhesions include a 2-3% incidence of small bowel obstruction, a decreased pregnancy rate and chronic abdominal pain. Moreover, during reoperations, the need for adhesiolysis results in a 6% incidence of iatrogenic bowel injury, increased operative time, and a longer and more complicated convalescence.[3] A longer duration of adhesiolysis and severe adhesions are associated with a higher incidence of postoperative complications.[4]
Little is known about risk factors for the formation of peritoneal adhesions. Reported studies are small or of limited current relevance.[5, 6] Repeat surgery within the first 3 months has been related to severe adhesions than surgery beyond this time.[7-9] However, the influence of the time interval between surgeries on the extent and severity of postsurgical adhesions is a topic of debate. Other risk factors that seem to impact the severity of adhesions are a history of peritonitis and presence of intra-peritoneal mesh.[10]
A recent systematic review has shown that anti-adhesive barriers are effective in reducing complications of adhesions.[11] It is important for clinical decision making and the optimal implementation of anti-adhesive strategies to understand which patients and which types of operations are at risk for developing more severe adhesions. Additionally, this could improve preoperative counseling and operative room strategy. A comprehensive assessment of risk factors for prolonged and difficult adhesiolysis is challenging due to the wide variety of abdominal incisions and procedures used in clinical practice. A median laparotomy is a common route in both acute and elective open general abdominal surgery and is considered to be adhesiogenic.[12] In this study, we used a large prospective patient cohort to assess the impact of different clinical variables on adhesiolysis time needed to gain access to the peritoneum, and on the severity of adhesions in patients undergoing a repeat median laparotomy.

Methods

We utilized data from consecutive patients who underwent a repeat median laparotomy and participated in the prospective LAPAD study ('LAParotomy or LAParoscopy and Adhesions study', clinicaltrials.gov registration number: NCT01236625). This study was approved by the local medical ethics committee, and was conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul). Detailed methods of the LAPAD study have been recently reported.[4] The LAPAD study included all patients admitted to the surgical ward of the Radboud University Medical Center for elective laparotomy or laparoscopy, thereby entering the peritoneal cavity, between June 2008 and June 2010. Demographic data, pre-operative surgical factors, and medical factors were prospectively collected. Demographic data collected were sex, age, body mass index, smoking status, and the number of pack-years. Preoperative medical

factors collected were long-term usage of corticosteroids, other immunosuppressive drugs and statins. Indications for the current operation were categorized as malignancy, ventral hernia, inflammatory bowel disease, or other indications. Pre-operative surgical factors included were the number of previous laparotomies and laparoscopies and the time interval between the preceding and the current median laparotomy. Additionally, the anatomical location of previous surgery, a history of peritonitis (defined as any generalized infection of the peritoneum), history of intra-peritoneal chemotherapy, and history or presence of an intra-peritoneal mesh were collected and analyzed as binary variables accounting for the cumulative operative history. The time interval between laparotomies was collected as a continuous outcome; however, we used a categorical variable (0-3 months, 4-6 months, 7-12 months, ≥12 months) in the analysis. Shorter time periods, for example a reoperation within 1 month, would result in numbers per category that are too low for meaningful comparison. For incision length of the current operation we used a categorical variable (e.g. upper, lower, and complete midline incision).

During surgery, detailed information regarding adhesions and adhesiolysis was collected through direct observation by a trained researcher who did not take part in the operation. Adhesions were graded according to the Zühlke classification, shown in table 1.[13] The Zühlke grade of adhesions was not included in the multi-variable analysis for risk factors for a longer duration of adhesiolysis because it cannot be determined pre-operatively. According to the definition of the Zühlke classification, adhesiolysis-related complications mostly occur in the presence of grade 3 and 4 adhesions.[4] Therefore we transformed the classification into a binary variable by merging grade 0, 1 and 2 (no or mild adhesions) and grade 3 and 4 (severe adhesions). The time needed for adhesiolysis was measured in minutes. Since the need for adhesiolysis in other parts of the abdomen varies depending on clinical circumstances, we only used adhesiolysis time needed to gain entry to the peritoneal cavity in our analysis. The incidences of iatrogenic enterotomy and seromuscular bowel injury during the duration of surgery were also collected for all patients. Iatrogenic enterotomy was defined as any unintended full-thickness bowel defect during the operation. A seromuscular injury was defined as an injury to the serosal and muscular layers of the bowel without visualization of the bowel lumen or spillage of bowel contents. The incidences of enterotmy and seromuscular injury presented, are the incidences during the complete operation. These findings were immediately recorded into a database by the researcher present in the operating room.

Statistical methods

Continuous variables are presented as means with standard deviaton, or as medians with interquartile range in case of a non-normal distribution. Dichotomous or categorical variables are presented as absolute numbers and percentages.

Table 1 Zühlke classification.

Zühlke grade	Adhesion description	Severity of adhesions
0	No adhesions	No, or only mild adhesions
1	Filmy adhesions, easy to separate by blunt dissection	
2	Adhesions with beginning vascularization, blunt and partly sharp dissection necessary	
3	Adhesiolysis possible by sharp dissection only, clear vascularization	Severe adhesions
4	Adhesiolysis possible by sharp dissection only, damage of organs hardly preventable	

A univariable ANOVA analysis was performed to assess the correlation between the duration of adhesiolysis and demographic, pre-operative surgical and medical variables. All variables, with a p-value of ≤0.05 were then analyzed using a multivariable independent ANOVA analysis, with the exception of the Zühlke grade of adhesions. The coefficient (b), the p-value, and the 95% confidence interval are shown for all variables. A p-value of ≤ 0.05 was considered to be statistically significant.

We used a univariable logistic regression analysis to identify risk factors for the development of severe adhesions. All variables with a p-value of ≤0.05 were then analyzed using a multivariable logistic regression analysis with forced entry. The odds ratio with 95% confidence interval and the p-value are presented. A p-value of ≤ 0.05 was considered statistically significant.

We excluded cases with missing data from the analysis. Statistical analyses were conducted using SPSS for Windows version 20.0 (SPSS, Chicago, IL).

Results

The LAPAD database consists of 755 operations carried out in 715 patients. 260 of these patients underwent a repeat median laparotomy. One patient was excluded due to a missing Zühlke score; thus, the analysis was performed using data from 259 patients. Demographic, pre-operative surgical and medical data are presented in table 2. The 94 (36%) patients with other benign indications for surgery are a heterogeneous group, comprising colostomy reversal in 11 (4%) patients and one patient due to a diaphragmatic hernia amongst other indications. 15 (6%) patients underwent their repeat median laparotomy within 0 to 3 months, of which only 1 (0.4%) patient within the first month. 26 (10%) patients underwent a repeat median laparotomy within 4 to 6 months, 61 (24%) patients within 7 to 12 months and 157 (61%) after 12 months.

Table 2 Baseline patient characteristics *mean ± SD, † median, IQR 25 -75, ‡ range, ¥ all abdominal wall operations were laparotomies where the peritoneal cavity was opened, Δ only one (0.4%) patient required a laparotomy within one month.

Patient factors	Included patients (N = 259)
Sex	
Male	146 (56%)
Female	113 (44%)
Age*	57.4 ± 13.8
Body mass index*	25.6 ± 4.6
Smoking status	
Nonsmoker	87 (34%)
Ex-smoker	110 (43%)
Smoker	62 (24%)
Number of pack years†	10.6 (0 – 28.6)
Medication	
Corticosteroids	14 (5%)
Other immunosuppressive agents	15 (6%)
Statins	53 (21%)
Number of previous laparotomies	
1	82 (32%)
2 or 3	114 (26%)
≥4 (4 – 56)‡	63 (42%)
Previous laparoscopy (1 – 2)‡	36 (14%)
History of peritonitis	73 (28%)
Presence or history of an intra-peritoneal mesh	31 (12%)
Mesh without anti-adhesive coating	21 (8%)
Mesh with anti-adhesive coating	3 (1%)
Type of mesh unknown	7 (3%)
Anatomical location of previous surgery	
Upper gastrointestinal tract	23 (9%)
lower gastrointestinal tract	204 (79%)
Hepato-biliary-pancreatic	33 (13%)
Abdominal wall¥	76 (29%)
Female reproductive tract	47 (18%)
Urological tract	36 (14%)
History of emergency laparotomy	58 (22%)
Time to Relaparotomy	
0-3 months$^{\Delta}$	15 (6%)
4-6 months	26 (10%)
7-12 months	61 (24%)
>12 months (13 – 624)‡	157 (61%)

Table 2 Continued.

Patient factors	Included patients (N = 259)
Indication for surgery	
Malignancy	61 (24%)
Ventral hernia	91 (35%)
Inflammatory bowel disease	18 (7%)
Other	94 (36%)
Incision used	
Lower median incision	95 (37%)
Upper median incision	60 (23%)
Complete median incision	104 (40%)

In 98% patients the complete previous incision was used for gaining access. Adhesions underneath the incision were absent in 29 patients (11%); 76 patients (29%) had grade 1 and 2 adhesions, 108 patients (42%) had grade 3 adhesions, and 46 patients (18%) had grade 4 adhesions. Median adhesiolysis time to gain entry in the abdomen was 10 minutes (5 – 25). During the total duration of surgery, an iatrogenic enterotomy occurred in 37 (14%) patients, whereas a seromuscular injury was noted in 95 patients (37%) (table 3).

Table 3 Adhesion-related outcome measures, † median, IQR 25 -75.

Total adhesiolysis time underneath incision in minutes†	10 (5 – 25)
Zühlke score of adhesions underneath incision	
0 (no adhesions)	29 (11%)
1 and 2	76 (29%)
3	108 (42%)
4	46 (18%)
Number of patients with an iatrogenic enterotomy	37 (14%)
Number of patients with an iatrogenic seromuscular injury	95 (37%)

Table 4 shows median adhesiolysis time to gain entry in the abdomen, the severity of adhesions and the number of previous laparotomies stratified for patients with no organ injury, seromuscular injury and enterotomy.

Table 4 Patient characteristics stratified for the severity of iatrogenic organ injury † median (IQR 25 – 75), ‡ the presented incidences, are the incidences during the complete operation.

	No organ injury (n = 151)	Seromuscular injury‡ (n = 71)	Enterotomy‡ (n = 37)	p
Total adhesiolysis time underneath incision in minutes †	7 (3 – 15)	18 (10 – 30)	23 (13 – 38)	<0.01
Severity of adhesions				<0.01
No, or mild adhesions	84 (56%)	17 (24%)	4 (11%)	
Severe adhesions	67 (44%)	54 (76%)	33 (89%)	
Number of previous laparotomies				<0.01
1	59 (39%)	19 (26%)	4 (11%)	
2 or 3	70 (46%)	26 (37%)	18 (49%)	
≥4	22 (15%)	26 (37%)	15 (40%)	

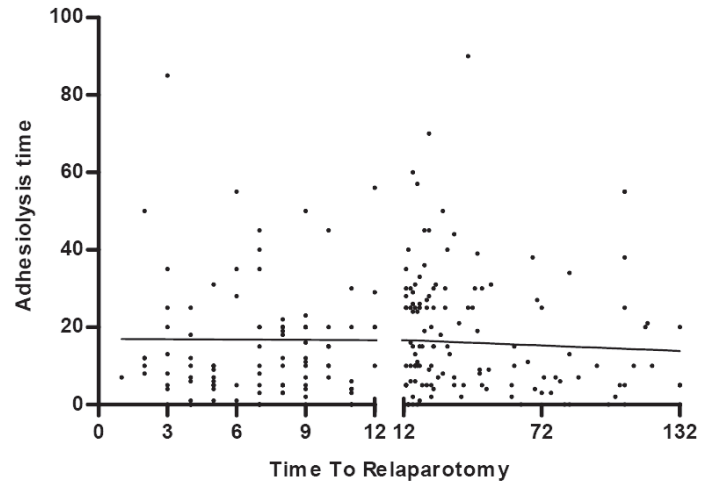
Risk factors for adhesiolysis time required to gain access to the peritoneum

In the univariable analysis, the number of previous laparotomies, ventral hernia as the indication for surgery, a history of peritonitis, history of intraperitoneal mesh or mesh still in situ, previous surgery on the lower gastro-intestinal tract or abdominal wall, a previous emergency laparotomy, and use of a complete midline incision significantly increased adhesiolysis time. In contrast, corticosteroid use and malignancy as the indication for surgery significantly correlated with a shorter adhesiolysis time (supplement 1).

Figure 1 shows a scatterplot of the time interval between surgeries plotted against adhesiolysis time needed to gain entry to the abdomen. The coefficient of the linear regression line is -0.02 (CI= -0.045 - -0.002) showing a significant but weak inverse correlation (p= 0.03).

In the multi-variable analysis, four or more previous laparotomies (p ≤0.01; CI 2.72 – 13.81), a complete midline incision (p ≤0.01; CI 5.48 – 13.49) and a history or presence of intraperitoneal mesh (p 0.01; CI 2.31 – 15.05) remained as significant independent risk factors for a longer duration of adhesiolysis underneath the incision (table 5). History of peritonitis, previous surgery on the lower gastrointestinal tract or abdominal wall were not independent risk factors for increased adhesiolysis time in the multi-variable analysis.

Figure 1 Correlation of time between laparotomies (in months) and adhesiolysis time (in minutes). The left side of the figure includes patient who underwent a repeated laparotomy within 12 months, the right side shows patients who underwent a repeated laparotomy.



Risk factors for more severe adhesions underneath the incision

The number of previous laparotomies, ventral hernia as the indication for surgery, a history or presence of an intra-peritoneal mesh, previous emergency laparotomy and previous surgery on the abdominal wall were significant risk factors for severe adhesions in the univariable logistic regression analysis (supplement 2).

In the multivariable logistic regression analysis, the only remaining significant risk factor for severe adhesions was a history of four or more previous laparotomies (p ≤0.01; OR 4.18). There was a trend toward severe adhesions in patients with a previous emergency laparotomy (p= 0.07; OR 1.96) (table 6).

Table 5 Multivariable analysis showing the effect of patient factors on adhesiolysis time required to gain access to the peritoneum, † reference category, ‡ p= <0.05.

Patient factors	B adjusted	95% Confidence interval		P adjusted
		Lower	Upper	
Medication				
Corticosteroids	-4.78	-12.22	2.67	0.21
Indication for surgery				
Ventral hernia	-0.40	-4.55	3.74	0.85
Malignancy	-2.09	-6.45	2.27	0.35
Number of laparotomies in history				
1†				
2 or 3	0.52	-3.74	4.78	0.81
≥4	8.27	2.72	13.81	≤0.01‡
Previous laparoscopy	-0.88	-5.92	4.16	0.73
Peritonitis in history	1.89	-2.25	6.03	0.37
Intra-peritoneal mesh	8.68	2.31	15.05	0.01‡
Type of previous surgery				
Lower gastrointestinal tract	1.93	-2.66	6.52	0.41
Abdominal wall	-1.83	-6.69	3.03	0.46
History of emergency laparotomy	0.13	-4.31	4.57	0.95
Type of incision used current laparotomy				
Lower median incision†				
Upper median incision	-0.47	-5.11	4.17	0.84
Complete median incision	9.48	5.48	13.49	≤0.01‡

Table 6 Multivariable analysis of the effect of surgical and medical factors on the severity of adhesions, † reference category, ‡ p= <0.05.

Patient factors	OR	95% CI OR		p
		Lower	Upper	
Number of previous laparotomies				
1†				
2 or 3	1.02	0.56	1.85	0.96
4 or more	4.18	1.73	10.11	≤ 0.01‡
Intra-peritoneal mesh	1.1	0.35	3.41	0.87
Anatomical location of previous surgery				
Abdominal wall	1.87	0.83	4.23	0.13
History of emergency laparotomy	1.96	0.95	4.03	0.07
Indication for surgery				
Ventral hernia	1.15	0.60	2.18	0.68

Discussion

Four or more previous laparotomies, a history or presence of an intra-peritoneal mesh, and the requirement of a complete midline incision were found to be independent risk factors for a longer duration of adhesiolysis. If all of these factors were present in a single patient in this study, an average of 41 minutes of adhesiolysis time would be required to gain access to the abdomen. The only independent risk factor for more severe adhesions was the number of previous laparotomies. Surprisingly, a shorter time interval between median laparotomies, a history of peritonitis, and the anatomical location of previous surgery did not prolong adhesiolysis. These factors were also not associated with more severe adhesions.

This is a large and unique prospective cohort study with an accurate and comprehensive assessment of pre-operative surgical and medical factors in a group of patients who have undergone one or more median laparotomies. While transverse incisions have gained popularity in colorectal fast-track surgery, a median laparotomy is still the incision of choice in many settings, including emergency laparotomy, open stoma formation, small bowel surgery, and open aortic reconstruction procedures. We assessed risk factors for both the duration of adhesiolysis and the severity of adhesions underneath the incision because the duration itself depends on the extent of the adhesions present. Duration of adhesiolysis may therefore be a more complete marker for operative difficulty while clearing the midline incision site from adhesions in order to gain entry to the abdomen. We decided not to include severity of adhesions in the multivariable analysis for the duration of adhesiolysis because adhesion severity cannot be determined pre-operatively. Progress has been made to locate adhesions by non-invasive means before surgery, however these techniques have not been fully developed for its standard use.[14]

We assessed 16 potentially relevant pre-operative factors for adhesion formation underneath the incision. However, we were unable to collect detailed data from the patients' medical history that might impact adhesion formation, such as previous use of anti-adhesive barrier and data on abdominopelvic radiation. The latter would most likely regard pelvic radiation of gynecological malignancies which impacts pelvic adhesion formation more than adhesions underneath the incision. Missing data on previous use of anti-adhesive barriers is unlikely to affect the results because routine usage of barriers is very uncommon in the Netherlands.[15] The indication and type of previous operations could be reliably assessed from medical records and are considered relevant based on the relation between the type of surgical procedure and incidence of adhesive small bowel obstruction.[3] In our study, however, the type of previous surgery was not found to be an independent risk factor for duration of adhesiolysis or for severe adhesions underneath the incision, illustrating that risk factors may differ between these two sequelae of adhesion formation.

Our results support earlier findings that repeated laparotomies increase adhesiolysis time by approximately 10 to 15 minutes.[5, 16] These studies, consisting of smaller

populations undergoing colorectal surgery, did not differentiate between the number of previous laparotomies, and did not analyze potentially relevant surgical or medical factors for a longer duration of adhesiolysis or severe adhesions. A cross-sectional study of 448 patients with previous surgery showed an association between a greater number of adhesions throughout the abdomen and multiple previous abdominal operations.[10] We consider adhesiolysis time a more clinically relevant endpoint than the number of adhesions throughout the abdomen because the number alone may not complicate subsequent surgery.[10] The same study showed a comparable incidence to our study of the most severe adhesions, underscoring the finding that around 10% of patients with previous surgery are at risk for organ injury during adhesiolysis. Patients in the same study, who have had intestinal leakage or an abdominal abscess, had significantly more adhesions.[10] Congruently, we found a significant correlation between a history of peritonitis and a longer duration of adhesiolysis in the univariable analysis. However, after correcting for other medical and surgical factors, this effect did not remain significant. More severe peritonitis might evoke more extensive and severe adhesions, potentially lengthening adhesiolysis time. Unfortunately, data on the severity or extent of previous peritonitis were not available for our patients. Specific emergency laparotomies, such as damage control surgery, could lead to more severe adhesion formation due to increased peritoneal injury. However, we were unable to specify the various indications for an emergency laparotomy due to their low incidence.

Our findings suggest that more extensive and repeated injuries to the peritoneum with subsequent adhesiolysis leads to a more aggressive reformation of adhesions. Limited evidence suggests that the local expression of growth factors associated with adhesion formation, and of proteins regulating fibrinolysis, is increased in the peritoneum of patients with adhesions, potentially leading to aggravated adhesion reformation.[17, 18]

This study unexpectedly showed that a shorter time interval between laparotomies does not correlate with a longer duration of adhesiolysis or with more severe adhesions. The adhesiolysis time needed to gain entry to the abdomen remained constant in the first year, and declined only marginally after ten years. Although the regression line was significant, the coefficient was low, reducing the clinical relevance of this finding. This result differs from a small retrospective study on the timing of the reversal of Hartmann's procedure, in which a difference in the severity of adhesions was found between patients undergoing a relaparotomy before 15 weeks versus after 15 weeks.[7] Given the small sample of patients who underwent a repeat median laparotomy within three months in this study and our study, caution must be taken when interpreting these findings. Due to the same reason, only 1 (0.4%) patient underwent a repeat median laparotomy within one month, this study cannot answer the question if a reoperation within 1 month is associated with a longer duration of adhesiolysis.

The results of this study can be used to improve patient counseling and operating room strategy. Patients with a history of multiple laparotomies should be counseled regarding the risks of a prolonged and more difficult operation, and a subsequent increased risk of organ injury. The scheduled operative time for these patients can be increased if deemed necessary. Furthermore, if a laparoscopic procedure is considered, an open introduction should preferably be performed outside the prior incision.

Using anti-adhesive barriers during repeat operations and after adhesiolysis seems to be less effective than primary prevention.[18, 19] Given the adhesiogenic nature of a median laparotomy, and given that repeat surgeries in the abdomen are likely to occur during a patients' lifetime, using an anti-adhesive barrier at initial laparotomy might be most beneficial for the patient.

Conclusion

This study demonstrates that four or more previous laparotomies, the presence or history of synthetic intra-peritoneal mesh, and the requirement of a complete midline incision independently prolonged the duration of adhesiolysis needed to gain access to the abdomen. Additionally, four or more previous laparotomies increased adhesion severity underneath the incision.

Supplement 1 Showing the effect of patient factors on adhesiolysis time *continuous variable with pearson's correlation coefficient, † reference category, ‡ p= <0.05.

Patient factors	B	Standard error	P	95% Confidence interval	
				Lower	Upper
Sex	3.45	1.86	0.07	-0.25	7.2
Age*	0.01*	0.06	0.938	-0.10	0.12
Body Mass Index*	0.10*	0.08	0.10	-0.04	0.25
Smoking status					
Non-smoker†					
Ex-smoker	2.12	2.22	0.35	-2.57	6.24
Smoker	0.14	2.48	0.96	-4.37	5.46
Packyears*	0.05*	0.06	0.45	-0.08	0.18
Medication					
Corticosteroids	-7.85	1.96	≤0.01‡	-11.56	-3.80
Other immunosuppressive agents	-2.10	5.90	0.75	-10.41	10.73
Statins	-1.54	2.30	0.50	-5.91	3.35
Indication for surgery					
Ventral hernia	5.12	1.91	0.01‡	1.27	8.72
Malignancy	-6.25	1.83	≤0.01‡	-9.97	-2.61
Inflammatory bowel disease	2.04	5.49	0.72	-7.85	13.46
Other	-0.89	1.97	0.66	-4.52	3.30
Number of previous laparotomies					
1†					
2 or 3	3.72	2.08	0.08	-.37	7.81
≥4	14.31	2.40	<0.01‡	9.57	19.04
Previous laparoscopy	4.46	2.26	0.05	-0.17	8.83
History of peritonitis	6.39	2.33	0.01‡	1.71	11.01
Intra-peritoneal mesh	12.01	3.97	≤0.01‡	4.62	20.26
Anatomical location of previous surgery					
Upper gastrointestinal tract	1.70	2.78	0.56	-3.96	7.04
Lower gastrointestinal tract	4.49	2.06	0.04‡	0.16	8.63
Hepato-biliary-pancreatic	4.50	2.86	0.11	-0.10	10.52
Abdominal wall	6.62	2.27	≤0.01‡	2.44	11.21
Female reproductive tract	-0.04	2.25	0.98	-4.24	4.71
Urological tract	-3.54	2.15	0.1	-7.26	1.28
History of emergency laparotomy	5.86	2.49	0.02‡	1.03	10.62
Time to Relaparotomy					
0-3 months†					
4-6 months	-8.41	6.41	0.18	-21.4	4.17
7-12 months	-5.22	5.97	0.38	-17.28	5.55
>12 months	-2.99	5.94	0.60	-15.16	8.10
Type of incision used during current laparotomy					
Lower median incision†					
Upper median incision	-1.03	1.70	0.55	-4.60	2.21
Complete median incision	12.26	2.11	≤0.01‡	8.12	16.78
Zühlke classification					
No adhesions					
Zühlke classification 1 and 2	8.08	1.16	≤0.01‡	5.67	10.3
Zühlke classification 3	16.61	1.19	≤0.01‡	14.07	18.94
Zühlke classification 4	33.22	2.94	≤0.01‡	27.91	39.53

Supplement 1 Continued.

Supplement 2 The effect of surgical and medical factors on the severity of adhesions
*continuous variable, † reference category, ‡ p= <0.05.

Patient factors	B	Standard error	P	OR	95% CI OR	
					Lower	Upper
Sex	-0.12	0.255	0.96	0.99	0.599	1.629
Age*	0.01	0.009	0.19	1.01	0.99	1.03
BMI*	-0.02	0.03	0.57	0.99	0.93	1.04
Smoking status						
Non-smoker†						
Ex-smoker	0.23	0.29	0.44	1.26	0.71	2.23
Smoker	0.14	0.34	0.68	1.15	0.59	2.22
Packyears*	0.002	0.01	0.74	1.002	0.99	1.01
Medication						
Corticosteroids	-0.71	0.56	0.20	0.49	0.17	1.46
Other immunosuppressives	0.33	0.56	0.56	1.39	0.46	4.12
Statins	-0.25	0.31	0.43	0.78	0.43	1.44
Indication for surgery						
Ventral hernia	0.57	0.27	0.04‡	1.77	1.03	3.02
Malignancy	-0.46	0.30	0.12	0.63	0.35	1.12
Inflammatory bowel disease	0.93	0.58	0.11	2.53	0.81	7.90
Other	-0.41	0.26	0.12	0.67	0.40	1.11
Number of previous laparotomies						
1†						
2 or 3	0.24	0.29	0.41	1.27	0.72	2.24
4 or more	1.89	0.42	≤ 0.01‡	6.62	2.89	15.14
Previous laparoscopy	0.66	0.40	0.1	1.93	0.89	4.19
History of peritonitis	0.37	0.29	0.20	1.45	0.83	2.55
Intra-peritoneal mesh	0.95	0.45	0.04	2.59	1.01	6.24
Anatomical location of previous surgery						
Upper gastrointestinal tract	0.07	0.45	0.89	1.07	0.44	2.56
Lower gastrointestinal tract	0.54	0.31	0.79	1.71	0.94	3.12
Hepato-biliary-pancreatic	0.20	0.39	0.60	1.22	0.57	2.61
Abdominal wall	0.98	0.30	≤ 0.01‡	2.66	1.47	4.82
Emergency laparotomy	0.96	0.34	0.01‡	2.60	1.34	5.04
Female reproductive tract	0.23	0.33	0.50	1.25	0.65	2.41
Urological tract	0.08	0.37	0.83	1.08	0.53	2.23
Time to relaparotomy						
0-3 months	-1.01	0.70	0.15	0.36	0.09	1.44
4-6 months	-0.65	0.64	0.31	0.52	0.15	1.83
7-12 months	-0.61	0.61	0.31	0.54	0.17	1.78
>12 months †			0.55			

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Chapter 7

Preoperative predictors for bowel injury during adhesiolysis

Richard ten Broek, MD, PhD; Chema Strik, MD; Harry van Goor, MD, PhD, FRCS
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
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Abstract

Background: Inadvertent bowel injury during adhesiolysis is a major cause of increased morbidity and mortality following abdominal surgery. Identification of risk factors predicting this complication would guide preoperative counselling and surgical decision-making. The aim of this study was to identify predictive preoperative factors for inadvertent bowel injury occurring during adhesiolysis.

Methods: All patients undergoing elective abdominal surgery between June 2008 and June 2010 were evaluated prospectively as part of the LAPAD study. Data on adhesiolysis and inadvertent organ injury were gathered by direct observation during operation. Univariable logistic regression was used to investigate factors that increased the risk of inadvertent bowel injury. Independent predictors of bowel injury were identified using multivariable logistic regression and used to create a clinical nomogram. Registration number: NCT01236625 (http://www.clinicaltrials.gov).

Results: Of 715 patients eligible for analysis, 48 (6.7 per cent) had inadvertent bowel injuries. In 42 patients the defect was detected during operation and in nine at a later time (3 patients had both). Bowel resection was required for almost two-thirds of the enterotomies. The number of previous laparotomies, anatomical site of the operation, presence of bowel fistula and laparotomy via a pre-existing median scar were independent predictors of bowel injury. A clinical scoring system was constructed using a nomogram incorporating these risk factors; this had a predictive discrimination, measured as the area under the receiver operating characteristic curve, of 0.85.

Conclusion: A nomogram based on four independent factors predicted the risk of inadvertent bowel injury.

Introduction

Adhesion formation is the most important long-term complication of abdominal surgery, with a lifelong risk of developing a variety of clinical conditions including small bowel obstruction, infertility and chronic pain.[1;2] A possibly more important consequence of adhesion formation is the difficulty encountered during repeat surgery.[3;4] Adhesiolysis increases operating time and has an adverse effect on the patient's convalescence, especially if a bowel injury occurs.[5-7] The incidence of accidental bowel injury is as high as 10–20 per cent in patients undergoing adhesiolysis.[4;6] The sequelae of bowel injury include unplanned bowel resections, an increase in the incidence of surgical complications, admission to an intensive care unit and even an increase in mortality. The mortality rate from bowel injury is estimated at between 8 and 50 per cent, depending on whether or not the defect was recognized during the operation.[4-6;8;9] The authors have demonstrated previously that bowel injuries occur more often in patients who require extensive adhesiolysis, those with high adhesion scores or a history of multiple laparotomies, and patients who have had lower abdominal procedures.[4;6;7] Most of these factors are not known before operation, but become apparent during the procedure. Estimating the risk of adhesiolysis-related complications, based on preoperative variables, would enable the risks and benefits of surgery for the individual patient to be taken into consideration; this information could be used during counselling, and to identify those who might benefit from the use of adhesion barriers.[10;11]

The aim of this study was to define preoperative predictors of bowel injury from data collected in a large prospective cohort of patients undergoing elective abdominal surgery. The authors also investigated whether a meaningful clinical scoring system could be developed to predict the risk of bowel injury.

Methods

This prospective observational study was carried out as part of the LAParotomy or LAParoscopy and Adhesiolysis (LAPAD) study (registration number NCT01236625; http://www.clinicaltrials.gov). The manuscript was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[12] Detailed information on the LAPAD methods has been published previously.[4;7] The executive board of the institutional review board confirmed that the study was exempt from its approval. The LAPAD study was designed to assess the incidence and impact of adhesiolysis on perioperative and postoperative complications.

Patient inclusion and data collection

All adult patients scheduled for elective abdominal surgery between 1 June 2008 and 2 June 2010 at the Department of Surgery, Radboud University Nijmegen Medical Centre, were screened for inclusion. The inclusion criterion was an elective laparotomy

or laparoscopy. Exclusion criteria were age under 18 years and mental disorder. Patients were included after giving oral and written informed consent.
Patient, surgical and medical data were assessed prospectively before, during and after hospital stay, and from the outpatient clinic for 6 months after discharge. During surgery, detailed information on adhesions, adhesiolysis and inadvertent organ damage were collected through direct observation by a trained researcher who did not take part in the operation.

Variables ~~analysed~~

Preoperative data on demographics, patient history, medication, operative risk scores and the planned procedure were extracted from the database for analysis. Demographics analysed comprised: sex, age, body mass index, smoking habits, and alcohol abuse based on the Alcohol Use Disorders Identification Test score.[13] Variables extracted from the patient's history included: laparotomies, laparoscopies, interval since last laparotomy, history of other surgery (and, if yes, what type of surgery), exploratory laparotomy, peritonitis, diabetes mellitus, inflammatory bowel disease and active malignancy. Medications included: corticosteroids, immunosuppressants, non-steroidal anti-inflammatory drugs, opioids and statins. The following operative risk scores were assessed: American Society of Anesthesiologists fitness classification, Portsmouth modification of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM) and Revised Cardiac Risk Index. Aspects of the planned operation included: anatomical site of operation, median incision through a pre-existing scar, previous surgery at the anatomical site of the operation, resection of bowel fistula, surgical experience, operative severity, mesh for ventral hernia repair *in situ* and surgical approach.
To facilitate calculations, the variable anatomical operation site was categorized as lower gastrointestinal, abdominal wall or miscellaneous, the latter comprising upper gastrointestinal, hepatopancreatobiliary and other abdominal surgery associated with a low incidence of bowel injury.

Assessment of outcome

Bowel injury was classified as inadvertent enterotomy or a delayed diagnosis of perforation. Inadvertent enterotomy was defined as any iatrogenic unintended full-thickness bowel defect detected during operation. Pre-existing fistulas or defects created while dissecting the bowel loop that harboured the fistula were not scored as an inadvertent enterotomy.
Delayed diagnosis of perforation was defined as a bowel defect with spill of gastrointestinal content that was diagnosed after surgery by imaging, at reoperation or at autopsy, and which was not explained by anastomotic leakage, bowel ischaemia or any other obvious causes of leakage unrelated to adhesiolysis.

Statistical analysis

For patients who had undergone several operations during the study interval, the most recent procedure was analysed and the others regarded as previous operations to avoid duplication of risk factors.
Univariable logistic regression was used to study the differences in demographics, patient history, medication, operative risk scores and the planned procedure between patients with and without bowel defects. The incidence of bowel injuries and crude odds ratios (ORs) with 95 per cent confidence intervals (c.i.) were calculated. All predictors found to be significant in univariable analysis were included in a multivariable analysis. A stepwise, backwards selection procedure was used with a P entry ≤ 0.100 and P stay ≤ 0.100. The adjusted OR was calculated with 95 per cent c.i. The R^2 value was computed to assess the information gained by addition of the co-variable(s) in the logistic regression model in comparison to a model without any co-variables. R^2 ranges between 0 and 100 per cent, with 0 per cent indicating that the prediction model explains none of the variability in the outcome data and 100 per cent indicating a perfect fit on the data.
The area under the receiver operating characteristic (ROC) curve (AUC) was used to quantify predictive discrimination. In general, these measures can be expected to be too high because the model was developed solely using the study sample, and this model would be expected to perform less adequately on a different random sample. Therefore, to evaluate the reliability of the created prediction model, an internal cross-validation was performed using bootstrap methods. The corrected R^2 and corrected AUC were calculated.
A nomogram was constructed using the multivariable prognostic model using the standard methods of the Regression Modelling Strategies package version 4.1-1 for R 2.12.0.[14] Such a nomogram can be used to predict bowel injury in an individual patient by filling in the values for each independent risk factor. The corresponding number of points can then be read from the scale presented. These are then summed to give a total point score, which is translated into a risk of enterotomy by using the two scales at the bottom of the nomogram. The 95 per cent c.i. of the predicted risk can be read from a 95 per cent c.i. plot of the estimated risks. The 95 per cent c.i. values were obtained by simulating 1000 draws for each combination of risk factors from the model's posterior distribution.
R version 2.12.0 (R Project for Statistical Computing, Vienna, Austria) was used for statistical analysis. $P < 0.050$ was considered statistically significant in all analyses.

Results

Of 844 consecutive elective operations that were eligible for inclusion, 89 were excluded for various reasons. Some 755 operations performed in 715 patients were available for analysis (Fig. 1). Most patients (62.9 per cent) were operated by one of 13 senior consultants participating in the study, 6.9 per cent by one of three junior consultants and 30.2 per cent by one of 31 residents. Bowel injuries occurred in 48 patients (6.7 per cent). In 42 patients a median of 1 (range 1–9) enterotomies was detected during the operation. A delayed perforation was diagnosed in nine patients. Three patients had both enterotomies detected during surgery and a delayed diagnosis of perforation.

A total of 73 enterotomies were detected in 42 patients. In 23 of these patients at least one of the enterotomies was made either under the incision, or during adhesiolysis between bowel and the abdominal wall. Eleven patients had an enterotomy in the left lower quadrant. The left upper quadrant and true pelvis was the location of an enterotomy in six and four patients respectively. Two patients had an enterotomy in the right half of the abdomen. Among the 42 patients with an enterotomy, the small bowel was lacerated in 28, the large bowel in nine, both small and large bowel in four, and one patient had a gastric enterotomy.

Impact of bowel injury

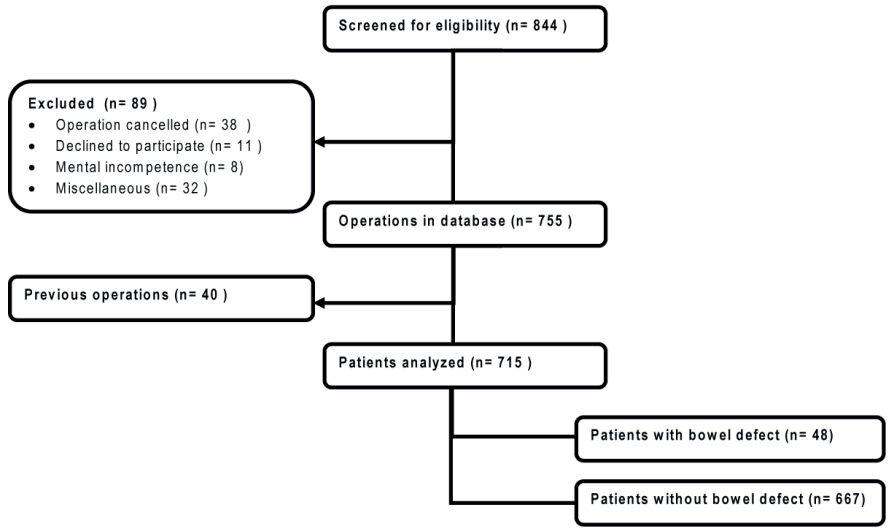
The mortality rate was higher in the bowel injury group than among those without bowel injury: 8 per cent (4 of 48) compared with 1.9 per cent (13 of 667) respectively ($P = 0.022$). All four patients who died in the bowel injury group had been diagnosed with a delayed perforation, and two also had an enterotomy detected during operation. One patient died after 4 days from ongoing abdominal sepsis after delayed perforation; the other three died from haemorrhage following relaparotomy, pneumosepsis or acute heart failure.

Enterotomy was followed by bowel resection in 26 of 42 patients, whereas enterotomies in the remaining patients were closed primarily. Thirteen of 48 patients with bowel injury required admission to an intensive care unit. Twenty-one patients (44 per cent) had one or more serious adverse events, which included abdominal sepsis (13 per cent), wound infection (17 per cent) and pneumonia (25 per cent).

Univariable analysis of risk factors for bowel injury

In univariable analysis, the number of previous laparotomies, and a history of surgery of the lower gastrointestinal tract, abdominal wall and urogenital tract were significant risk factors for bowel injury (Table 1; ~~Table S1, supporting information~~). Patients who had undergone a single laparotomy previously had only a moderately increased risk of bowel injury; this increased dramatically with additional laparotomies. The risk of bowel injury was also higher when a previous laparotomy had been carried out within

Figure 1 Flow chart of patients included in the study.



the previous 6 months. Patients with active malignancy had a lower risk of bowel injuries, but also had undergone fewer laparotomies previously.

A previous laparoscopy had no significant effect on the risk of bowel injury. The risk of enterotomy was highest in patients scheduled for surgery of the abdominal wall and lower gastrointestinal tract. The risk also increased when surgery was planned using a median incision through a pre-existing scar, was at the same anatomical location as previous operations, required fistula resection, or a mesh was *in situ* from a previous ventral hernia repair. None of the demographic variables, medications or operative risk scores had a significant effect on the risk of bowel injury.

Multivariable analysis of risk factors for bowel injury

In the multivariable analysis, four predictors were included in the final model (Table 2). A history of laparotomies was the strongest predictor of bowel injury, the risk increasing with each additional laparotomy. The anatomical site of planned surgery also had an independent impact on the risk of bowel injury. Other variables included in the multivariable model were fistula resection and a median incision through a pre-existing scar. The AUC as a measurement of the predictive discrimination of the model was 0.85 and the R^2 value was 25.8 per cent. After internal validation using bootstrapping, the AUC was 0.82 and R^2 was 20.7 per cent.

Table 1 Risk factors for bowel injury identified by univariable logistic regression analysis.

	No. of patients*	Odds ratio†	P
Patient history			
Laparotomies			
0	2 of 263 (0.8)	1.00 (reference)	< 0.001
1	5 of 186 (2.7)	3.61 (0.69, 18.79)	0.128
2 or 3	24 of 191 (12.6)	18.75 (4.38, 80.39)	< 0.001
≥ 4	17 of 75 (23)	38.25 (8.60, 170.15)	< 0.001
Lower GI surgery			
No	9 of 378 (2.4)	1.00 (reference)	
Yes	39 of 337 (11.6)	5.37 (2.56, 11.25)	< 0.001
Abdominal wall surgery			
No	31 of 582 (5.3)	1.00 (reference)	
Yes	17 of 133 (12.8)	2.61 (1.40, 4.86)	0.003
Urological surgery			
No	36 of 635 (5.7)	1.00 (reference)	
Yes	12 of 80 (15)	2.94 (1.46, 5.91)	0.003
Active malignancy			
No	40 of 375 (10.7)	1.00 (reference)	
Yes	8 of 340 (2.4)	0.20 (0.09, 0.44)	< 0.001
Peritonitis			
No	39 of 653 (6.0)	1.00 (reference)	
Yes	9 of 62 (15)	2.67 (1.22, 5.82)	0.013
Aspects of planned operation			
Anatomical site of operation			
Miscellaneous	4 of 270 (1.5)	1.00 (reference)	< 0.001
Lower GI	28 of 327 (8.6)	6.23 (2.16, 17.99)	0.001
Abdominal wall	16 of 118 (13.6)	10.43 (3.40, 31.94)	< 0.001
Repeated median laparotomy			
No	11 of 462 (2.4)	1.00 (reference)	
Yes	37 of 253 (14.6)	7.02 (3.51, 14.04)	< 0.001
Previous surgery at anatomical site			
No	12 of 448 (2.7)	1.00 (reference)	
Yes	36 of 267 (13.5)	5.66 (2.89, 11.09)	< 0.001
Resection of fistula			
No	39 of 683 (5.7)	1.00 (reference)	
Yes	9 of 32 (28)	6.46 (2.80, 14.90)	< 0.001
Mesh in situ			
No	40 of 672 (6.0)	1.00 (reference)	
Yes	8 of 43 (19)	3.61 (1.57, 8.30)	0.002

A nomogram was constructed to calculate the risk of bowel injury (Fig. 2) and 95 per cent c.i. of the predicted risk calculated (Fig. 3). Several clinical examples of how the model can be applied are provided in Table S3 (supporting information).

Table 2 Adjusted risk of bowel injury in multivariable logistic regression analysis. Values in parentheses are 95 per cent confidence intervals. GI, gastrointestinal.

	Adjusted odds ratio	P
History of laparotomies		
0	1.00 (reference)	< 0.001
1	2.27 (0.40, 12.97)	0.355
2 or 3	10.03 (2.04, 49.24)	0.005
≥ 4	15.79 (2.97, 83.91)	0.001
Anatomical site of operation		
Miscellaneous	1.00 (reference)	0.050
Lower GI	3.81 (1.26, 11.55)	0.018
Abdominal wall	2.57 (0.78, 8.44)	0.120
Fistula surgery		
No	1.00 (reference)	
Yes	2.34 (0.95, 5.74)	0.064
Repeat median laparotomy		
No	1.00 (reference)	
Yes	1.99 (0.89, 4.44)	0.094

Figure 2 Nomogram to calculate the risk of enterotomy. Draw a vertical line for each variable to the 'points' axis at the top. Sum the points for the four variables and locate this total score on the 'total points' axis. Draw a vertical line from this through the bottom two scales to determine the linear predictor and the predicted risk of enterotomy. GI, gastrointestinal.

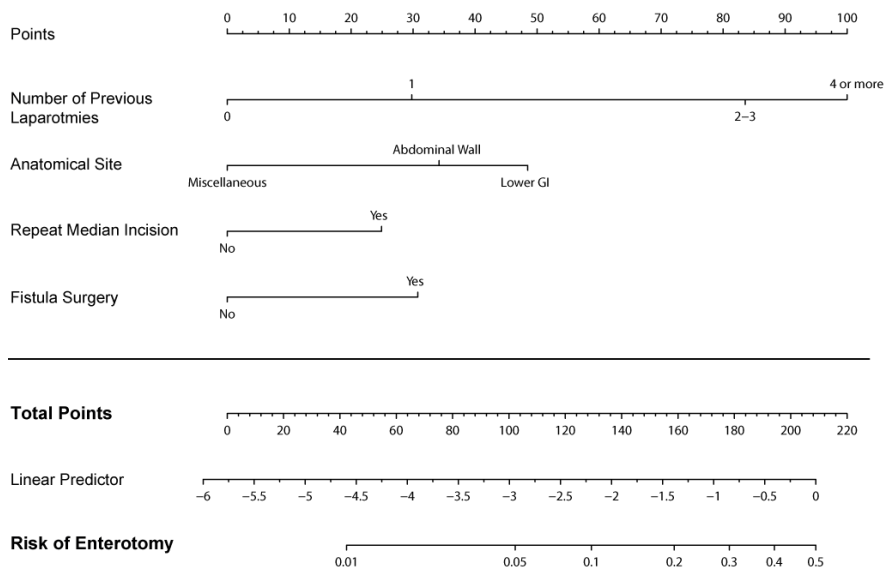
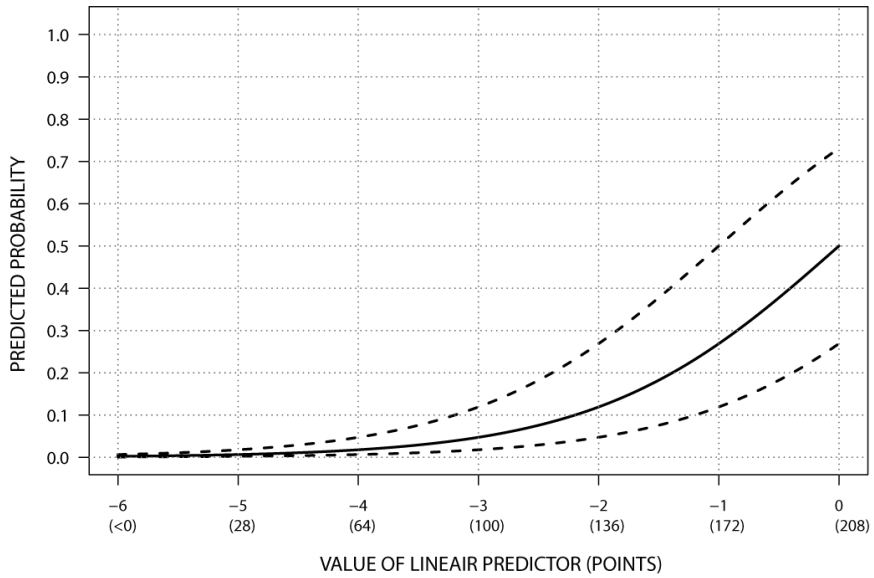


Figure 3 The predicted risk of enterotomy and 95 per cent confidence interval obtained by simulation.



Discussion

This study identified four predictors of adhesiolysis-related bowel injury. Using the nomogram built on this prediction model, the risk of inadvertent bowel injury can be estimated for an individual patient. The risk estimate can be used to inform the patient about their risk of bowel injury during adhesiolysis when obtaining informed consent. In addition, the surgeon can use the information to weigh up the benefits and risks of surgery. The prediction model demonstrated good internal validation, with comparable AUC and R^2 values after bootstrapping. The predicted risks of bowel injury ranged from 0 to 50 per cent.

This large prospective cohort study was designed specifically to assess complications of adhesiolysis by direct observation, thereby guaranteeing data accuracy, which enabled the search for risk factors related to adhesiolysis injury. Previous studies had to rely on medical records, which are often inaccurate when reporting adhesive complications.[15-17] The present results were obtained using robust statistical methods and were validated internally using bootstrapping.

Although this prediction model shows a good fit, it only identifies groups with low and moderate risk of bowel injury, with predicted risks ranging between 0 and 50 per cent. The inability to predict incidences above 50 per cent is most likely due to the many

operative aspects that can result in bowel injury, the absence from the present data of other potentially relevant risk factors, and unknown risk factors such as the variation among humans in the extent and severity of adhesion formation after a similar insult. It is questionable whether prediction of complications after surgery could ever reach 100 per cent considering the interaction of multiple patient, surgeon and local environmental factors. Recently a prediction model for development of surgical-site infection found an incidence ranging from 15.6 to 36.1 per cent; a model predicting the need for blood transfusion in head and neck surgery yielded rates ranging from 0.5 to 62 per cent.[18;19] The present model identified predictive factors that are easily assessed from the history of all elective surgical patients. This enables the prediction model to be validated in external populations.

In this study, previous laparoscopic surgery was not identified as a risk factor for bowel injury. This finding should be interpreted with caution because of the low incidence of major previous laparoscopic procedures in this series. There are limited data showing less adhesion formation and better adhesion-related clinical outcome with gynaecological laparoscopy and other minor general surgical procedures.[20] Evidence regarding laparoscopic colorectal surgery is not convincing, particularly because adhesion formation was assessed *post hoc* or as a secondary outcome in colorectal studies.[21;22]

Other potential preoperative factors for prediction of adhesion-related complications are the use of adhesion barriers, and mapping of adhesions to the abdominal wall and between viscera.[11] Adhesion barriers were barely used in any of the previous operations in the present cohort, consistent with the low use of barriers reported in surveys.[10;23] Adhesion mapping was not included as a variable here because such diagnostic tools are still experimental.[24-26] No routine diagnostic tool exists that can reliably assess adhesions before surgery, especially those between viscera.

Two previous retrospective studies provided evidence that the number of previous laparotomies increases the risk of bowel injury at adhesiolysis.[6;17] In these studies age was also a risk factor, which could not be confirmed in the present cohort. Other risk factors identified in the present study had either not been analysed previously or did not show a significant effect.[6;16;27]

Some variables identified as potential risk factors in univariable analysis were not significant in the final multivariable risk model, including history of peritonitis, mesh *in situ* and time since last laparotomy, which have been associated with more dense and extensive adhesions in other studies.[7;28-31] Numbers in these subgroups might have been too small to demonstrate significance.

There was no difference in the risk of bowel injury between senior and junior consultants, and residents. However, high-risk patients were often scheduled for surgery by a consultant (or at least with a consultant available to assist), which might have obscured the impact of surgical experience in this observational study.

Although the statistical background of the risk model presented is complex, patients at risk of bowel injury are easily identified using the nomogram based on the four predictive factors from the multivariable model. Fewer than 10 per cent of surgeons inform their patients about the risks of adhesions.[10] Given the high risk of morbidity and increased perioperative mortality associated with bowel injuries, not informing patients about these risks could be deemed negligent.[32] The present results may be used to weigh up the risks and benefits of surgery for the individual patient. Most patients undergoing abdominal surgery have a vital (oncological) indication for surgery. However, many others with benign conditions undergo abdominal surgery to improve quality of life (ventral hernia with mainly cosmetic complaints). In these patients, the potential benefits of the operation and the risk of reducing quality of life owing to bowel injury can now be discussed more appropriately. Having identified a high-risk patient, precautions can be taken, such as scheduling extra operating theatre time, and recruiting a dedicated consultant and operating room team.

Future studies are needed to evaluate whether reduction of adhesion formation by the use of adhesion barriers can decrease the risk of bowel injury during reoperations.[11;33]

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Chapter 8

Risk factors for future repeat abdominal surgery

Chema Strik, M.D.; Martijn W.J. Stommel, M.D., PhD; Laura J. Schipper, M.D.;
Prof. Harry van Goor, M.D., PhD, FRCS; Richard P.G. ten Broek, M.D., PhD
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
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Abstract

Purpose: Today, 40 to 66% of elective procedures in abdominal surgery are reoperations. Reoperations show increased operative time and risk for intra- and postoperative complications, mainly due to the need to perform adhesiolysis. It is important to understand which patients will require repeat surgery for optimal utilization and implementation of anti-adhesive strategies. Our aim is to assess the incidence and identify risk factors for repeat abdominal surgery.

Methods: This is the long-term follow-up of a prospective cohort study (LAPAD study; clinicaltrials.gov: NCT01236625). Patients undergoing elective abdominal surgery were included. Primary outcome was future repeat abdominal surgery and was defined as any operation where the peritoneal cavity is reopened. Multivariable logistic regression analysis was used to identify risk factors.

Results: 604 (88%) out of 715 patients were included, median duration of follow-up was 46 months. 160 (27%) patients required repeat abdominal surgery and underwent a total of 234 operations. The indication for repeat surgery was malignant disease recurrence in 49 (21%), incisional hernia in 41 (18%) and indications unrelated to the index surgery in 58 (25%) operations. Older age (OR 0.98; p 0.002) and esophageal malignancy (OR 0.21; p 0.034) significantly reduced the risk of undergoing repeat abdominal surgery. Female sex (OR 1.53; p 0.046) and hepatic malignancy as indication for surgery (OR 2.08; p 0.049) significantly increased the risk of requiring repeat abdominal surgery.

Conclusions: One in four patients will require repeat surgery within 4 years after elective abdominal surgery. Lower age, female sex and hepatic malignancy are significant risk factors for requiring repeat abdominal surgery.

Introduction

An increasing number of patients undergo abdominal surgery multiple times during their lifetime, due to a higher life expectancy and advances in surgical technology this is expected to increase even further.[1, 2] Today, as many as 40 to 66% of elective procedures in general surgery are reoperations.[3-5] It is estimated that 10 to 37% of patients undergoing elective abdominal surgery will require repeat abdominal surgery and might thus benefit from the use of anti-adhesive barriers.[6, 7] During reoperations, the need for adhesiolysis results in increased operative time, a six to ten percent incidence of inadvertent bowel injury and a longer and more complicated convalescence. The risk for bowel injuries is amplified by each consecutive laparotomy and can be as high as 50%.[8] Furthermore, increased postoperative mortality and higher healthcare costs are reported especially when adhesiolysis resulted in bowel injury.[5, 9]

It is important to understand which patients will require repeat surgery for the optimal resource utilization and implementation of anti-adhesive strategies in order to reduce adhesiolysis-related complications. A recent systematic review and meta-analyses of four commercially available anti-adhesive barriers demonstrated that these barriers effectively reduce the incidence and severity of adhesions and operative time.[10]

Currently, it is unknown which patients are at risk for undergoing repeat abdominal surgery. The risk of repeat abdominal surgery has only been investigated in a number of disease specific cohorts which assessed risk factors for undergoing repeat surgery for disease recurrence.[11, 12] Population-based studies only focused on the incidence and did not provide patient specific risk factors for undergoing repeat surgery.[6, 7]

The aim of this study is to analyze patterns of repeat abdominal surgery during long-term follow-up and identify risk factors for requiring repeat abdominal surgery in a cohort of patients undergoing elective abdominal surgery.

Material and methods

Study design and patients

This is a follow-up study of the prospective LAPAD study ('LAParotomy or LAParoscopy and Adhesions study', clinicaltrials.gov registration number: NCT01236625). Detailed methods of the LAPAD study are reported recently.[5] The LAPAD study included all patients admitted to the surgical ward of the Radboud university medical center for elective laparotomy or laparoscopy between June 2008 and June 2010. Demographics, pre-operative surgical factors and medical patient factors were prospectively collected. Patients who deceased within 30 days after discharge of the index admission were excluded from this study. Data on endpoints were gathered from 30 days after discharge until November 2013. For patients with multiple operations included in the LAPAD study, data was gathered from the last included operation. Patients and their general practitioners were contacted separately and a questionnaire was sent regarding admissions to the departments of surgery for hospitalization for repeat

abdominal surgery and episodes of bowel obstruction. Data was collected from medical records of hospitals and nursing homes when applicable. A waiver was obtained from the medical ethical committee of the Radboud university medical center (registration number: 2013/097) for this study.

Variables

Baseline demographics included sex, age, body mass index, American Society of Anesthesiologists classification, P-Possum score, presence of malignancy, number of previous laparotomies (0, 1 or 2, ≥3) and laparoscopies (0 and 1 or more), anatomical location of previous surgery and index operation (lower gastro-intestinal, abdominal wall, other) and surgical approach (median, subcostal, other incision, and laparoscopy). Data on intra-operative factors collected were adhesiolysis time (0-30, ≥31 minutes), complete adhesiolysis defined as all peritoneal adhesions lysed, severity of adhesions underneath the incision, operative area and other abdominal areas according to the Zühlke classification[13] comprising 0, 1 and 2 as no or mild adhesions and 3 and 4 as severe adhesions, the location of adhesions (upper and lower abdomen) any iatrogenic organ injury due to adhesiolysis, estimated blood loss and the creation of an ostomy at the end of surgery. Postoperative data collected was the incidence of any intra-abdominal complication within 30 days of the index operation, comprising intra-abdominal sepsis, abscess, anastomotic leakage, fistula, delayed diagnosed perforation, hemorrhage and a relaparotomy or relaparoscopy.

Endpoints

Repeat abdominal surgery was defined as any operation were the peritoneal cavity is opened. In this study we analyzed reoperations during the long-term follow-up (after 30 days from discahrge). Immediate reoperations for serious adverse events of the index operation have previously been described.[5] Repeat abdominal surgeries were categorized in a planned or an unplanned operation. Planned repeat operations were defined as all repeat operations that are part of a staged treatment strategy (e.g. closure of a protective loop ileostomy, or staged resection of synchronous hepatic metastasis from a colorectal carcinoma in situ). An operation was defined as unplanned if it was not part of the initial treatment strategy. The number of laparotomies and laparoscopies, the time interval between last included surgery and repeat abdominal surgery, surgical approach (open or laparoscopic), anatomical location and indication for repeat surgery were registered. Indications for repeat abdominal surgery were categorized as malignant disease recurrence comprising both loco-regional recurrence and distant metastasis, incisional or parastomal hernia, emergency laparotomy, adhesive small bowel obstruction or adhesiolysis for abdominal pain, ostomy closure including loop ileostomy closure, relocation of ostomy, new ostomy creation for any reason, new malignancy and other indications. For patients who

required multiple operations, the date, surgical approach and indication for surgery were registered separately.

Statistical methods

Continuous variables are presented as means with standard deviation, or medians with interquartile range if non-normal distribution. Dichotomous or categorical variables are presented as absolute numbers and percentages.

Univariable and multivariable logistic regression analysis was performed to identify risk factors for unplanned repeat abdominal surgery. All variables, with a p-value of ≤0.10 were analyzed using a multivariable logistic regression analysis with stepwise backwards selection, P entry ≤0.10 and P stay ≤0.10. The odds ratio, the 95% confidence interval of the odds ratio and the p-value of risk factors are presented. The area under the receiver operating characteristic (ROC) curve (AUC) was used to quantify the predictive value of the logistic regression analysis.

A Kaplan-Meier analysis was performed showing the cumulative hazard risk of patients requiring repeat abdominal surgery over time.

A value of $p \leq 0.05$ was considered significant. Statistical analysis was performed using SPSS for Windows version 20.0 software (SPSS, Chicago, IL). There was only minimal missing data, thus we excluded per analysis those cases with missing data.

Results

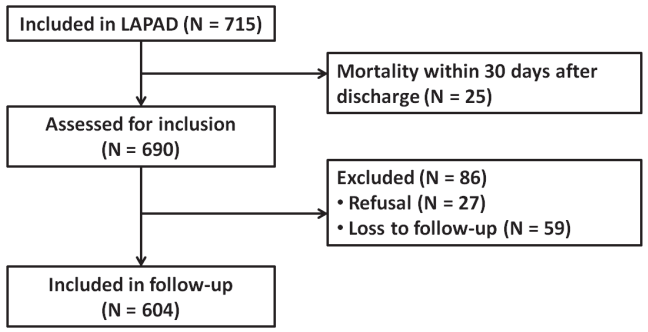
715 patients were eligible for inclusion in this study, 25 patients died within 30 days after discharge of the index admission terminating their follow-up. Out of 86 patients that were excluded, 27 patients declined to participate in follow-up and 59 patients were lost to follow-up, leaving 604 (88%) patients for inclusion (Figure 1). The median duration of follow-up was 46 (IQR 33 – 54) months.

Baseline characteristics at index operation and incidence of repeat abdominal surgery

Table 1 shows the baseline characteristics. Mean (SD) age was 59 (± 14) and 343 (57%) patients were male. A median incision was used in 392 patients, a subcostal in 86 and other incisions were used in 70 patients, whereas a laparoscopic procedure was performed in 56 patients. Severe adhesions in the operative area were seen in 187 (31%) of the patients. An ostomy was created in 107 (17%) patients. 53 (9%) patients developed a postoperative intra-abdominal complication.

Patients that were excluded were significantly younger (mean 55 years of age versus 59 years; p 0.04), had more often a diagnosis of inflammatory bowel disease (17 (20%) versus 65 (11%); p 0.01) and had less often an esophageal malignancy (4 (5%) versus 85 (14%); p 0.02) in comparison to patients included in the follow-up study. Other baseline characteristics did not show significant differences (results not shown).

Figure 1 Flow-chart.



The incidence and characteristics of repeat abdominal surgery are shown in Table 2. 160 (27%) patients underwent a total of 234 repeat abdominal operations, 108 (18%) Patients had 1 laparotomy, 29 (5%) had 2 laparotomies, 16 (3%) patients underwent 3 or more laparotomies and 14 (2%) patients required a laparoscopy. 196 (84%) Operations were unplanned and 38 operations were staged procedures of which 32 (84%) were loop ileostomy closures. 134 (22%) Patients underwent at least one unplanned repeat abdominal operation. The anatomical location of repeat surgery was most often the lower gastrointestinal tract in 98 (45%) and abdominal wall in 49 (23%). The indication for repeat surgery was malignant disease recurrence in 49 (21%), incisional or parastomal hernia in 41 (18%) and other indications in 58 (25%) operations. Other indications comprised predominately of open or laparoscopic cholecystectomy (28% of other indications), results not shown. 3 patients required a protective loop ileostomy during an unplanned repeat operation, which needed subsequent closure. The cumulative incidence of repeat abdominal surgery after 2 years is 20% (figure 2).

Table 1 Baseline characteristics.

Patient factors	Number of patients (N = 604)
Sex	
Male	343 (57%)
Female	261 (43%)
Age*	59 ± 14
BMI*	25.7 ± 4.4
Smoking status	
Non-smoker	77 (34%)
Ex-smoker	111 (50%)
Smoker	36 (16%)
Physiologic-Possum score†	16 (14 – 20)
ASA-score	
1	104 (17%)
2	370 (61%)
3	130 (22%)
Diagnosis of IBD	65 (11%)
Number of previous laparotomies	
0	220 (36%)
1 or 2	255 (42%)
≥3	129 (21%)
Previous laparoscopy	
Yes	531 (88%)
No	73 (12%)
Anatomical location previous surgery	
Upper GI	31 (5%)
Lower GI	291 (48%)
Abdominal Wall	115 (19%)
HPB	66 (11%)
Other	200 (33%)
Malignancy as indication for surgery	
Colorectal	108 (18%)
Hepatic	68 (11%)
Esophageal	42 (7%)
Other	85 (14%)
Benign indication for surgery	
Ventral hernia	104 (17%)
Fistula	35 (6%)
Other	194 (32%)
Anatomical location index operation	
Lower GI	264 (44%)
Abdominal Wall	102 (17%)
Other	238 (39%)
Surgical approach	
Median	392 (65%)
Subcostal	86 (14%)
Other	70 (12%)
Laparoscopy	56 (9%)

Table 1 Continued.

Patient factors	Number of patients (N = 604)
Presence of adhesions	
Yes	379 (63%)
No	225 (37%)
Adhesiolysis time (minutes)	
0-30	474 (79%)
>31	130 (21%)
Adhesion severity underneath incision	
No or mild adhesions	419 (70%)
Severe adhesions	178 (30%)
missing data	7 (1%)
Adhesion severity operative area	
No or mild adhesions	407 (69%)
Severe adhesions	187 (31%)
Missing data	10 (2%)
Adhesion severity other abdominal areas	
No or mild adhesions	460 (78%)
Severe adhesions	127 (22%)
Missing data	17 (3%)
Iatrogenic organ injury due to adhesiolysis	148 (25%)
Ostomy created	
Ileostomy	69 (11%)
Colostomy	38 (6%)
Wound classification	
Clean	237 (39%)
Clean-contaminated	325 (54%)
Contaminated	39 (7%)
Dirty	3 (1%)
Length of surgery	202 (145 – 269)
Intra-abdominal complication	53 (9%)
Relaparotomy	51 (9%)

Table 2 The number of patients that underwent repeat abdominal surgery as well as the anatomical location and indication of repeat abdominal surgery. * three patients required the formation of a protective loop ileostomy during a reoperation and subsequent closure.

Repeat surgery	
Patients undergoing repeat surgery	
Yes	160 (27%)
No	444 (73%)
Patients undergoing unplanned repeat surgery	
Yes	134 (22%)
No	470 (78%)
Number of laparotomies	
1	108 (18%)
2	29 (5%)
≥3 (3-5)	16 (3%)
Laparoscopy	
Yes	14 (2%)
No	590 (98%)
Number of planned operations	38 (16%)
Closure protective loop ileostomy	32
Staged resection synchronous colorectal metastasis	3
Ileo-anal pouch	2
Colostomy reversal	1
Number of unplanned operations	196 (84%)
Anatomical location	
Upper GI	5 (2%)
Lower GI	98 (45%)
HPB	35 (16%)
Abdominal Wall	49 (23%)
Vascular	3 (1%)
Other	27 (13%)
Indication repeat surgery	
Malignant disease recurrence	49
Incisional/parastomal hernia	41
Emergency laparotomy	19
Adhesion-related surgery	11
Ostomy closure	
Protective loop ileostomy*	35
Colostomy	1
Ileo-anal pouch	3
Relocation ostomy	14
Ostomy creation	2
New malignancy	5
Other	58
Department performing the operation	
Surgery	225
Gynecology	5
Urology	4

Figure 2 Cumulative risk over time for requiring repeat abdominal surgery, straight black line represents the mean cumulative incidence, the dashed line represents the 95% confidence interval of the mean cumulative incidence.

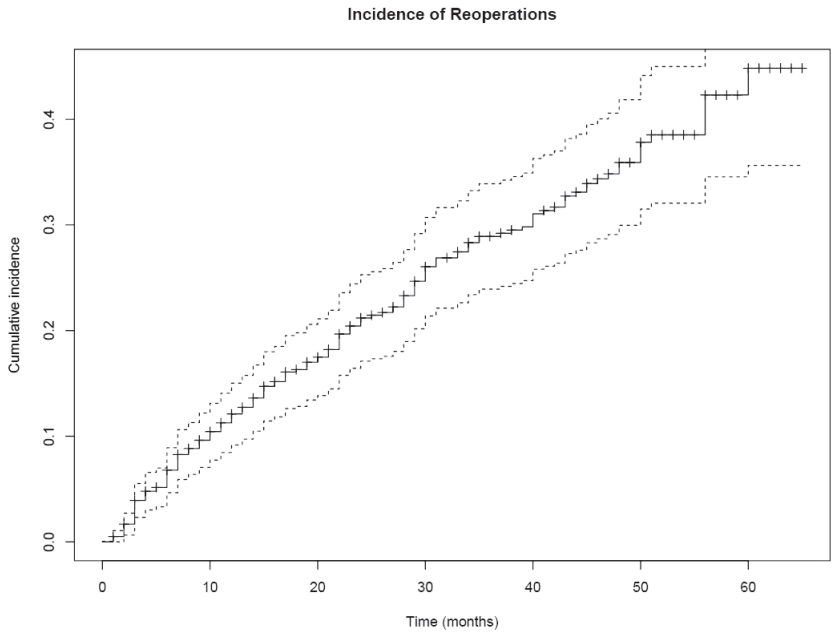


Table 3 shows the incidence of unplanned repeat abdominal surgery stratified for the anatomical location of the index operation, demonstrating that the abdominal wall (25%) and lower gastro-intestinal tract (24%) have the highest incidence, although this did not reach a statistical significant difference (p = 0.53).

Table 3 The incidence of unplanned repeat abdominal surgery stratified for anatomical location of index operation.

Unplanned repeat abdominal surgery	Anatomical location of index operation				
	Upper GI	Lower GI	HPB	Abdominal Wall	Other
No	59 (84%)	200 (76%)	82 (79%)	77 (76%)	52 (81%)
Yes	11 (16%)	64 (24%)	22 (21%)	25 (25%)	12 (19%)

Univariable logistic regression for risk factors of requiring unplanned repeat abdominal surgery

Female gender (OR 1.60; p 0.02), severe adhesions underneath the incision (OR 1.54; p 0.04), at the operative area (OR 1.53; p 0.04) and other abdominal areas (OR 1.62; p 0.03) and an iatrogenic enterotomy (OR 2.19; p 0.03) were significantly associated with an increased risk for undergoing repeat abdominal surgery. Three or more previous laparotomies (OR 1.61; p 0.07), lower gastrointestinal tract as the anatomical location of previous abdominal surgery (OR 1.44; p 0.07), hepatic malignancy as indication for surgery (OR 1.67; p 0.07), more than 30 minutes of adhesiolysis (OR 1.47; p 0.09) and intra-abdominal complications (OR 1.65; p 0.07) showed a trend towards an increased risk for repeat abdominal surgery. Higher age (OR 0.98; p <0.01), higher Physiologic Possum score (OR 0.94; p 0.01), esophageal malignancy (OR 0.16; p 0.01) and laparoscopic surgery (OR 0.40; p 0.04) were significantly associated with a reduced risk for undergoing repeat abdominal surgery. A trend for reduced risk for repeat abdominal surgery was seen for patients with an ASA-score of 3 (OR 0.58; p 0.10), (supplement 1) .

Multivariable logistic regression for risk factors for undergoing unplanned repeat abdominal surgery

Female sex (OR 1.53; p 0.046) and hepatic malignancy as indication for surgery (OR 2.08; p 0.049) were significantly associated with an increased risk for undergoing unplanned repeat abdominal surgery. Older age (OR 0.98; p 0.002), esophageal malignancy (OR 0.21; p 0.034) and laparoscopic surgery (OR 0.26; p 0.007) were significantly associated with a reduced risk of undergoing repeat abdominal surgery. The area under the curve, representing the predictive value of the variables incorporated in the multivariable logistic regression analysis was 0.67 (95% CI 0.62 – 0.72).

Table 4 Multivariable logistic regression analysis with backward selection for unplanned repeat surgery; Nagelkerke R2 = 0.091.

Patient factor	OR	95% CI OR		p
Sex				
Male	Ref			
Female	1.53	1.01	3.18	0.046
Age	0.98	0.96	0.99	<0.01
Hepatic malignancy	2.08	1.00	4.33	0.049
Esophageal malignancy	0.21	0.05	0.89	0.034
Surgical approach				
Median	ref			
Subcostal	0.56	0.26	1.16	0.119
Other	0.92	0.50	1.70	0.785
Laparoscopy	0.26	0.10	0.69	0.007
Intra-abdominal complication	1.75	0.99	3.10	0.053

Discussion

Our results show that one in four patients will require repeat abdominal surgery within 4 years after elective abdominal surgery. Female sex and hepatic malignancy had an increased risk for unplanned repeat abdominal surgery. Older patients, patients undergoing laparoscopic surgery and patients with esophageal malignancy as the indication for surgery had a significantly lower risk for unplanned repeat abdominal surgery.

The incidence in our study, with a median of 4 years follow-up, was higher than that of a US population based study of predominantly colorectal procedures with a follow-up of two years (14%), but lower than a population based ten-year follow-up study of patients undergoing a first abdominal operation in Scotland in the year 1986 (36,7%), nicely demonstrating the effect of time on incidence of repeat surgery.[6, 7] In contrast to these studies, we utilized detailed and accurate baseline data of a prospective cohort study with real time assessment of the index operation, providing us with the opportunity to reliably assess the incidences of and the majority of risk factors for repeat abdominal surgery. Although our cohort is drawn from a tertiary referral center and therefore contains more complex abdominal surgery, the results of the above mentioned studies suggest that patients undergoing surgery in a secondary care hospital have a similar incidence of repeat abdominal surgery.

The attrition bias of this study is low with a 88% completed follow-up of patients included in the study. Although, there are significant differences at baseline, with regard to age, diagnosis of inflammatory bowel disease and esophageal malignancy, these differences are small which reflects the large sample size rather than meaningful

differences that would affect our results. Databases of Dutch general practitioners keep nearly complete medical records of patients, including correspondences from hospital admissions, making the results of our study very reliable.

Most data on risk factors for repeat operations, albeit scarce, are from studies in patients with a ventral hernia or inflammatory bowel disease that only report on repeat surgery for disease recurrence.[11, 12, 14, 15] This only accounts for approximately half of all repeat operations according to our results, meaning that previous studies suffer from underreporting of risk factors for repeat surgery in general. For patients with a ventral hernia, size of the defect, previous repair, and an open approach increased the risk of repeat surgery, whereas older age decreased the risk for recurrent hernia repair.[11, 15] Disease specific patient factors could improve the predictive value of our analysis, due to the heterogeneity of our population we did not incorporate all disease specific factors which is a limitation of our approach to include all types abdominal surgery in the study. Our study also showed that older age was correlated with a lower incidence of repeat abdominal surgery. Young patients have a higher life-time risk for developing new disease that may require abdominal surgery and are also more often fit for subsequent surgery, explaining that patients of older age have a reduced risk for requiring repeat surgery. Patients who have had a hepatic resection for a malignancy have about a twofold increased risk for a repeat operation. Most likely this will be a subsequent liver procedure because more than half of patients develop a recurrence within 2 years of whom 40% is eligible for a reoperation.[16, 17]

Patients who underwent a laparoscopic procedure had a significantly decreased risk for repeat surgery, however, only a small number of patients in this series underwent a laparoscopic procedure and these patients mostly had an uncomplicated medical history. This result should be interpreted with caution. Female gender was an independent risk factor for unplanned repeat abdominal surgery. This result is undoubtedly attributed to the risk of gynecological operations, and probably a higher incidence of gallstone disease and pelvic (floor) disorder in women.[18, 19]

Around 15% of the total amount of repeat abdominal operations were loop-ileostomy closures. It is debatable to consider loop ileostomy closures as repeat abdominal surgery, as they are viewed as minor procedures. However, during a loop ileostomy closure the peritoneum is opened and adhesiolysis might be necessary. Furthermore, a systematic review showed that the overall morbidity of a loop ileostomy closure is 17% and that 4% of patients undergoing a loop ileostomy closure require a laparotomy.[20] Therefore, we accounted loop ileostomy closures in our study as repeat abdominal surgery. Most ileostomy closures were staged procedures (91%) and were not incorporated in the analysis assessing risk factors for unplanned repeat abdominal surgery. In our cohort, 9% of the patients underwent a laparoscopic procedure, this is somewhat low compared to today's surgical practice. However, the most common indications for repeat abdominal surgery were malignant disease recurrence or other

indications, both are unaffected by the surgical approach of the index surgery. The incidence of a ventral hernia or a small bowel obstruction is lower after a laparoscopic procedure.[9, 21] However, the incidence of a ventral hernia is still 10.8% and the incidence of small bowel obstruction is 5.5% three years after laparoscopic surgery. In our study, these two indications comprise a minority of indications for requiring repeat abdominal surgery.

An important key finding in our study is that 9 out of 10 repeat operations are unplanned and almost half is unrelated to the index operation. These results cause a paradigm shift, implicating that the potential benefit of adhesion barriers is not confined to two-stage procedures and disease with known high risk for reoperations for small bowel obstruction or ventral hernia. The high rate of unplanned reoperations suggest a potential for adhesion barriers to reduce morbidity and healthcare costs due to adhesiolysis-related complications. The effectiveness of anti-adhesive barriers has been demonstrated in a systematic review and meta-analysis showing reduced operative time and a decreased incidence of adhesions up to 50%.[10, 22] The in-hospital costs are around 4500 U.S. Dollars higher for patients requiring adhesiolysis during surgery compared to patients not requiring adhesiolysis.[5] A study assessing the cost-effectiveness of anti-adhesive barriers showed that barriers costing 50£ would pay back the cost of its investment if it reduced adhesion-related readmissions for small bowel obstruction by 16%.[23] Even greater benefits might be gained from reducing adhesiolysis-related complications during repeat abdominal surgery and could be as high as 927 US Dollars after open surgery and 380 US Dollars after laparoscopic surgery.[5, 9, 24]

Our study showed most reoperations involve the lower gastrointestinal and hepatic-pancreatic-biliary tract and the abdominal wall. In general, younger patients and female patients might benefit most from anti-adhesive barriers, as they have the highest risk for unplanned reoperations. Patients undergoing a second hepatic resection suffer from increased operative time and a higher incidence of organ injury, mostly due to adhesiolysis.[25, 26] A clinical trial assessing the efficacy of an anti-adhesive barrier in two-stage hepatic resection found a reduction in the extent and severity of adhesions as well as a reduction in time needed to mobilize the liver. A trend was seen towards less postoperative complications after the second hepatic resection.[25] Patients who are operated upon because of a hepatic malignancy might benefit from placement of an anti-adhesive barrier around the liver because they have a two-fold increased risk for requiring repeat surgery, consisting mainly of repeat hepatic resections.

Conclusion

In our cohort, one in four patients will require repeat surgery within 4 years after elective abdominal surgery mostly due to malignant disease recurrence, incisional or parastomal hernia or reasons unrelated to the index operation. The lower gastrointestinal tract, hepato-pancreatico-biliary tract and the abdominal wall are anatomical locations predominately involved at repeat abdominal surgery. Lower age, females and patients with a hepatic malignancy show the greatest risk for requiring repeat abdominal surgery. Results may guide cost effective use of anti-adhesion barriers.

Supplement 1 Univariable logistic regression analysis for unplanned repeat surgery.

Patient factor	OR	95% CI OR		p
Sex				
Male	Ref.			
Female	1.60	1.09	2.35	0.02
Age	0.98	0.97	0.99	<0.01
BMI	0.97	0.92	1.01	0.13
Smoking status				
Non-smoker	Ref			
Ex-smoker	1.12	0.73	1.72	0.59
Smoker	0.87	0.49	1.54	0.64
Physiologic Possum score	0.94	0.90	0.98	0.01
ASA-score				
1	Ref			
2	0.92	0.56	1.53	0.75
3	0.58	0.30	1.10	0.10
Diagnosis of IBD	1.17	0.64	2.12	0.62
Number of previous laparotomies				
0	Ref			
1 or 2	1.39	0.88	2.17	0.16
≥3	1.61	0.96	2.71	0.07
Previous laparoscopy				
Yes	1.17	0.66	2.07	0.59
No	Ref			
Anatomical location previous surgery				
Upper gastrointestinal tract	0.83	0.34	2.08	0.70
Lower gastrointestinal tract	1.44	0.98	2.12	0.07
Abdominal Wall	1.23	0.77	1.98	0.39
HPB	0.76	0.39	1.46	0.41
Other	1.07	0.72	1.61	0.61
Malignancy as indication for surgery				
Colorectal	0.71	0.41	1.21	0.21
Hepatic	1.67	0.96	2.91	0.07
Esophageal	0.16	0.04	0.68	0.01
Other	0.79	0.44	1.41	0.42
Benign indication for surgery				
Ventral hernia	1.06	0.64	1.76	0.81
Fistula	1.66	0.79	3.49	0.18
Other	1.29	0.86	1.93	0.21
Anatomical location index operation				
Other	Ref			
Lower GI	1.37	0.89	2.11	0.15
Abdominal Wall	1.39	0.80	2.43	0.24

Supplement 1 Continued.

Patient factor	OR	95% CI OR		p
Surgical approach				
Median	Ref			
Subcostal	0.94	0.54	1.64	0.82
Other	1.15	0.64	2.06	0.82
Laparoscopy	0.40	0.17	0.96	0.04
Adhesiolysis time				
0-30	Ref			
≥31	1.47	0.94	2.29	0.09
Zühlke score underneath incision				
No or mild adhesions	Ref			
Severe adhesions	1.54	1.02	2.31	0.04
Zühlke score operative area				
No or mild adhesions	Ref			
Severe adhesions	1.53	1.02	2.30	0.04
Zühlke score other abdominal areas				
No or mild adhesions	Ref			
Severe adhesions	1.62	1.04	2.53	0.03
Iatrogenic injury due to adhesiolysis				
Enterotomy	2.19	1.07	4.47	0.03
Seromuscular injury	1.25	0.77	2.02	0.36
Other organ injury	1.18	0.56	2.49	0.66
Wound classification				
Clean	Ref			
Clean-contaminated	1.01	0.68	1.52	0.95
Contaminated	1.07	0.48	2.39	0.87
Dirty	1.78	0.16	20.00	0.64
Ostomy	1.41	0.87	2.27	0.16
Duration of surgery	1.00	1.00	1.00	0.41
Intra-abdominal complication	1.65	0.96	2.84	0.07
Relaparotomy	1.52	0.81	2.87	0.20

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Chapter 9

Long-term impact of adhesions on bowel obstruction

Chema Strik, M.D.; Martijn W.J. Stommel, M.D., PhD; Laura J. Schipper, M.D.;
Harry van Goor, M.D., PhD, FRCS; Richard P.G. ten Broek, M.D., PhD
Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
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Abstract

Background: The incidence of reoperation for adhesive bowel obstruction following general abdominal surgery is 2.5% and carries a considerable risk of mortality and morbidity. Adhesions account for 56% of all cases of bowel obstruction. Most epidemiological knowledge regarding adhesive bowel obstruction is derived from data of national registries and retrospective cohorts of elective abdominal surgery. Due to the design of these studies it remains unknown whether specific surgical factors impact the occurrence of bowel obstruction. We aimed to comprehensively assess risk factors for the incidence of adhesive bowel obstruction with emphasis on intra-operative surgical factors.

Methods: Follow-up study of the prospective LAPAD study (clinicaltrials.gov registration number: NCT01236625) including patients undergoing all types of elective open or laparoscopic abdominal surgery. Primary endpoint of this study was (suspected) adhesive bowel obstruction. Univariable and multivariable logistic regression analysis were used to assess risk factors.

Results: 604 (88%) of 715 patients could be included. A total of 38 (6%) patients experienced an episode of adhesive bowel obstruction. Surgery on the lower gastrointestinal tract (OR 4.57, p <0.01) and the severity of adhesions in the operative area (OR 2.37, p 0.04) independently increased the risk for adhesive small bowel obstruction.

Conclusion: Patients undergoing surgery on the lower gastrointestinal tract and patients with more severe adhesions present at surgery have an increased risk for adhesive bowel obstruction.

Introduction

Adhesion formation is the most common complication of abdominal and pelvic surgery and comprises a lifelong risk of bowel obstruction, difficulties during reoperations, female infertility and chronic abdominal pain.[1-3] The incidence of reoperation for adhesive bowel obstruction following general abdominal surgery is 2.5% and carries a considerable in-hospital mortality rate of 2.5%. The prevalence of medical and surgical complications is 8% and 6%, respectively.[1, 4, 5] Adhesions are the most common cause of bowel obstruction, accounting for 56% of all cases.[1] Surgery of the lower gastrointestinal tract seems the most important risk factor for the occurrence of adhesive bowel obstruction. Conflicting results have been found for many other demographic and particularly surgery related factors.[1, 6]

Most epidemiological knowledge regarding adhesive bowel obstruction is derived from data of regional and national registries and retrospective cohorts of acute surgery for bowel obstruction and elective abdominal surgery.[1] Due to the design of these studies it is unknown whether specific surgical factors, such as presence of adhesions, during elective abdominal surgery increase the risk of bowel obstruction.[7-11]

A large comprehensive prospective cohort study, performed by our group, showed that the need for adhesiolysis during repeat surgery resulted in an increased incidence of iatrogenic organ injury, increased operative time and a longer and more complicated convalescence.[2] These prospective data provided the opportunity to perform a follow-up study and to accurately assess the impact of specific surgical factors on the incidence of adhesive bowel obstruction in patients undergoing all types of elective abdominal surgery. We focused on the severity of adhesions and adhesiolysis data at initial surgery as potential surgical risk factors.

Methods

Study design and patients

This is a long-term follow-up study of the prospective LAPAD study ('LAParotomy or LAParoscopy and Adhesions study', clinicaltrials.gov registration number: NCT01236625). Detailed methods of the LAPAD study are reported.[2] The LAPAD study included all patients admitted to the surgical ward (no day care or short stay) of the Radboud university medical centre for elective laparotomy or laparoscopy between June 2008 and June 2010. Baseline data regarding demographics, pre-operative surgical factors, medical patient factors, intra-operative surgical factors and postoperative variables were prospectively collected at the time of the LAPAD study.

Patients that died within 30 days after discharge of the initial admission were excluded from this study. Data on the primary outcome measure was gathered retrospectively from 30 days after discharge until November 2013. Data was gathered from the last included surgery for patients with multiple abdominal surgeries included in the LAPAD study. Patients and their general practitioners were contacted separately and

a questionnaire was sent regarding admissions to departments of internal medicine or surgery for episodes of bowel obstruction and hospitalization for repeat abdominal surgery. Additionally, data was collected from medical records of hospitals and nursing homes when applicable. A waiver was received from the medical ethical committee of the Radboud university medical center (registration number: 2013/097) for this study. Patients admitted with a bowel obstruction were treated in accordance with local protocols, closely resembling the international guideline presented by Catena et al. [12] In general, patients were admitted to the hospital and managed conservatively with nasogastric tube decompression, intravenous fluids and an abdominal CT-scan within 48 hours. The conservative treatment was continued for a maximum of 72 hours. For patients showing signs of peritonitis, irreducible hernia or signs of strangulation, abdominal CT imaging and surgery was performed on the same day of admission.

Variables

The included baseline demographics comprise sex, age, Body Mass Index, American Society of Anesthesiologists classification[13], P-Possum score[14], presence of malignancy and a diagnosis of inflammatory bowel disease. Surgical factors included were the number of previous laparotomies (0, 1 or 2, ≥3) and laparoscopies (0 and 1 or more), anatomical location of previous surgery (upper gastrointestinal tract, lower gastrointestinal tract, abdominal wall, hepato-pancreato-biliary and other), anatomical location of index operation (lower gastro-intestinal, abdominal wall, other) and surgical approach (median, subcostal, other incision, and laparoscopy). Intra-operative factors collected were adhesiolysis time (0-30, ≥31 minutes), complete adhesiolysis defined as all peritoneal adhesions lysed, severity of adhesions underneath the incision, operative area and other abdominal areas according to the Zühlke classification[15] comprising 0, 1 and 2 as no or mild adhesions and 3 and 4 as severe adhesions, the location of adhesions (upper and lower abdomen) any iatrogenic organ injury due to adhesiolysis, estimated blood loss, the creation of an ostomy at the end of surgery and total operative time. Postoperative factors collected were the incidence of any intra-abdominal complication within 30 days of the index operation, comprising intra-abdominal sepsis, abscess, anastomotic leakage, fistula, delayed diagnosed perforation, hemorrhage and a relaparotomy or relaparoscopy.

Endpoints

The primary endpoint of this study was adhesive bowel obstruction, comprising both small bowel and colonic obstruction. Bowel obstruction was defined as no passage of feces with nausea, vomiting, cramping abdominal pain, absence of bowel movements and signs of abdominal distention at physical examination. The time interval between last surgery and bowel obstruction, duration of admission and treatment was registered. The causes of intestinal obstruction were categorized as

'definitely adhesive' if imaging (CT or MRI showing diagnostic signs suggestive of adhesive small bowel obstruction[16, 17]) or intra-operative findings showed adhesions as the cause. Bowel obstruction was defined as 'probably adhesive' when no other cause could be identified during the diagnostic work-up. Other causes included 'tumor' if an intra-abdominal tumor was the cause, 'incarcerated hernia' if bowel was trapped in an hernia and reduction was not possible and 'other cause' if another cause than the above mentioned pathologies caused the bowel obstruction. For patients with multiple episodes of bowel obstruction, the etiology was assessed per episode.

Statistical methods

Continuous variables are presented as means with standard deviaton, or medians with interquartile range (25 – 75) in case of a non-normal distribution. Dichotomous or categorical variables are shown as absolute numbers and percentages.

A univariable logistic regression analysis was performed to assess risk factors for patients with at least one adhesive bowel obstruction comprising 'definitively adhesive' and 'probably adhesive'. All predictors found to be significant in univariable analysis were considered for multivariable analysis due to the low incidence of adhesive bowel obstruction. For the multivariable logistic regression analysis, a stepwise backwards selection procedure was used with a P entry ≤0.10 and P stay ≤0.10. The adjusted OR was calculated with 95 per cent confidence interval. The R2 value was computed to assess the amount of variation explained by addition of the variables in the model.

A Kaplan-Meier analysis was performed calculating the cumulative hazard risk of adhesive bowel obstruction over time. For each independent risk factor derived from multivariable analysis a separate Kaplan-Meier analysis was done.

A p value of ≤ 0.05 was considered significant. Statistical analysis was performed using SPSS for Windows version 20.0 software (SPSS, Chicago, IL). There was only minimal missing data, thus we excluded per analysis the cases with missing data.

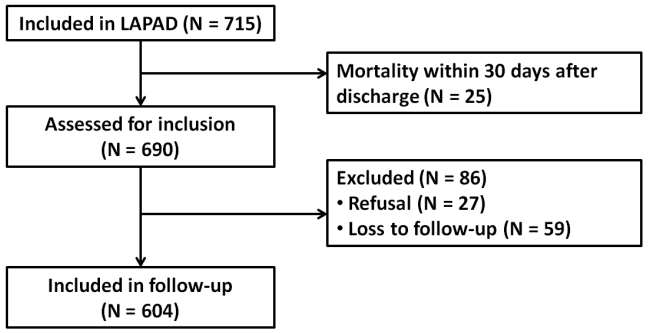
Results

715 patients were assessed for inclusion, 25 patients died during admission or within 30 days after discharge, 27 declined to participate, 58 did not respond and 1 patient was lost to follow-up. 604 (88%) patients were included in this study (figure 1). The median follow-up duration was 46 (IQR 33 – 54) months.

Baseline characteristics and incidence of bowel obstruction

Baseline characteristics, including missing data, are shown in table 1. 220 (36%) patients had no history of prior abdominal surgery, 255 (42%) had 1 or 2 and 129 (21%) patients had 3 or more previous abdominal operations. The anatomical location of the index operation was the lower gastrointestinal tract in 264 (44%), abdominal wall in 102 (17%) and other in 238 (39%) patients. Surgeries performed on the lower

Figure 1 Flow-chart.



gastrointestinal tract consisted mainly of right colectomy and sigmoid or rectal resections. The abdominal wall as anatomical location of surgery included principally the component-separation-technique with or without a mesh. The type of operations in the other anatomical locations category comprised mainly out of resection of the upper gastrointestinal tract and hepatic-biliary-pancreatic surgery and other types of surgery. In 379 (63%) patients the presence of adhesions was confirmed during the index procedure, 187 (32%) patients had severe adhesions in the operative area. Complete adhesiolysis was performed in 156 (27%) patients, 193 (33%) patients did not have complete adhesiolysis, for 30 patients it was unknown if adhesiolysis was complete. An ostomy was created in 107 (18%) patients.

A total of 58 (10%) patients experienced an bowel obstruction, 49 patients experienced 1 episode and 9 patients 2 or more episodes, reaching a total of 71 episodes of bowel obstruction. 38 (66%) of 58 patients had at least 1 episode of adhesive bowel obstruction. Seven patients had a recurrent episode of bowel obstruction after their first bowel obstruction. Five patients had a total of two episodes, one patient had three episodes and one patient had a total of five episodes of bowel obstruction. The cause of bowel obstruction was definitely adhesive in 11 (16%) episodes, probably adhesive in 37 (52%), tumor in 14 (20%), incarcerated hernia in 2 (3%) and other causes in 7 (10%) patients (table 2). Of the patients presenting with bowel obstruction caused by adhesions, one patient (3%) had an obstruction of the large bowel. Of the 58 patients that had an episode of bowel obstruction, 19 patients did not have adhesions at their index surgery. Of the 38 patients with an adhesive bowel obstruction only 10 patients did not have adhesions at their original surgery. Three out of ten patients with an adhesive bowel obstruction requiring surgery did not have adhesions at their original surgery.

The episode of bowel obstruction could be managed conservatively in 54 (76%) patients. 17 (24%) episodes were managed by an operation, due to adhesions in 10

Table 1 Baseline characteristics, * Mean ± Standard deviation, † Median IQR (25 – 75).

Patiënt factors	Baseline characteristics (n= 604)
Sex	
Male	343 (57%)
Female	261 (43%)
Age*	59 ± 14
BMI*	25.7 ± 4.4
Smoking status	
Non-smoker	212 (35%)
Ex-smoker	278 (46%)
Smoker	113 (19%)
P-Possum-score*	16 (14 – 20)
ASA-score	
1	104 (17%)
2	370 (61%)
3	130 (22%)
Number of previous laparotomies	
0	220 (36%)
1 or 2	255 (42%)
≥3	129 (21%)
Previous laparoscopy	
Yes	73 (12%)
No	531 (88%)
Anatomical location previous surgery	
Upper GI	31 (5%)
Lower GI	291 (48%)
Abdominal Wall	115 (19%)
HPB	66 (11%)
Other	200 (33%)
Malignancy as indication for surgery	
Yes	295 (49%)
No	309 (51%)
Diagnosis of inflammatory bowel disease	
Yes	65 (11%)
No	539 (89%)
Anatomical location index operation	
Lower GI	264 (44%)
Right colectomy	68 (26%)
Sigmoid or rectal resection	99 (38%)
Subtotal or proctocolectomy	32 (12%)
Other	65 (24%)
Abdominal Wall	102 (17%)
Other	238 (39%)
Upper GI	70 (29%)
HPB	104 (44%)
Other	64 (27%)

Table 1 Continued.

Patiënt factors	Baseline characteristics (n= 604)
Surgical approach	
Median	392 (65%)
Subcostal	86 (14%)
Other	70 (12%)
Laparoscopy	56 (9%)
Presence of adhesions	
Yes	379 (63%)
No	225 (37%)
Adhesiolysis time (minutes)	
0-30	474 (79%)
>31	130 (22%)
Complete adhesiolysis	
No adhesiolysis	225 (37%)
Yes	156 (26%)
No	193 (32%)
Missing data	30 (5%)
Adhesion severity underneath incision	
No or mild adhesions	419 (69%)
Severe adhesions	178 (30%)
Missing data	7 (1%)
Adhesion severity operative area	
No or mild adhesions	407 (67%)
Severe adhesions	187 (31%)
Missing data	10 (2%)
Adhesion severity other abdominal areas	
No or mild adhesions	460 (76%)
Severe adhesions	127 (21%)
Missing data	17 (3%)
Adhesions in the upper abdomen	
Yes	233 (39%)
No	352 (58%)
Missing data	19 (3%)
Adhesions in the lower abdomen	
Yes	275 (46%)
No	301 (50%)
Missing data	28 (4%)
Iatrogenic organ injury due to adhesiolysis	148 (24%)
Estimated blood loss† (ml)	450 (100 – 1013)
Ostomy created	
Ileostomy	69 (11%)
Colostomy	38 (6%)
Total operative time (min)	201 (144 – 269)
Intra-abdominal complication	53 (9%)
Relaparotomy	51 (8%)

episodes, due to an obstructing tumor in 4, incarcerating hernia in 2 and 1 was caused by a jejunostomy catheter. All patients with an adhesive bowel obstruction that required surgery were operated through an open incision. The median length of stay for patients admitted with a bowel obstruction was 6 days.

Table 2 Incidence of bowel obstruction, † Median IQR (25 – 75), ‡ range.

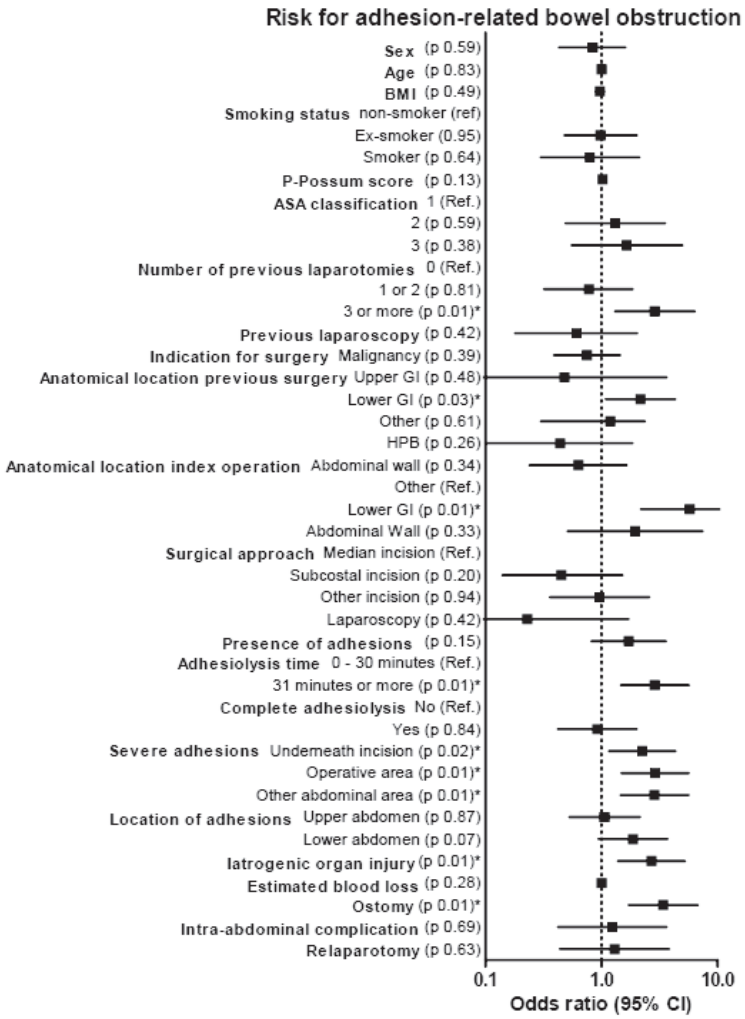
Bowel obstruction	Outcome
Patients with bowel obstruction	58 (10%)
Patients with adhesion-related bowel obstruction	38 (6%)
Episodes of bowel obstruction	
0	546 (90%)
1	49 (8%)
≥2 (2 – 5)‡	9 (2%)
Cause of obstruction	
Adhesions	
Definitely adhesive	11 (16%)
Most likely adhesive	37 (52%)
Tumor	14 (20%)
Incarcerated hernia	2 (3%)
Other	7 (10%)
Treatment	
Conservative	54 (76%)
Operative	17 (24%)
Length of hospital stay†	6 (4 – 11)

Univariable logistic regression for risk of adhesive bowel obstruction

Three or more previous laparotomies (95% CI OR 1.31 – 6.37, p= 0.01), lower gastrointestinal tract as the anatomical location of previous surgery (95% CI OR 1.09 – 4.33, p= 0.03), a diagnosis of inflammatory bowel disease (95% CI OR 1.53 – 7.19), lower gastrointestinal tract as the anatomical location of the index operation (95% CI OR 2.19 – 15.11, p 0.01), adhesiolysis time of >30 minutes during index operation (95% CI OR 1.47 – 5.67, p 0.01), severe (Zühlke grade 3 or 4) adhesions underneath the incision (95% CI OR 1.16 – 4.35, p <0.01), severe adhesions in the operative and other abdominal areas (95% CI OR 1.49 – 5.64, p <0.01 and 95% CI OR 1.46 – 5.65, p <0.01), iatrogenic organ injury due to adhesiolysis (95% CI OR 1.38 – 5.25, p <0.01) and creation of an ostomy during the index operation (95% CI OR 1.71 – 6.77, p 0.01) significantly increased the risk for (definitively and probably) adhesive bowel obstruction (Figure 2). A trend was seen towards an increased risk for adhesive bowel obstruction for adhesions located in the lower part of the abdomen (95% CI OR

0.94 – 3.71, p= 0.07). Complete adhesiolysis of the abdomen in comparison to non-complete adhesiolysis during the index operation did not reduce the risk for the occurrence of adhesive bowel obstruction (95% CI OR 0.42 – 2.01, p= 0.84). Post-operative intra-abdominal complications did not increase the risk for adhesive bowel obstruction (95% CI OR 0.42 – 3.64, p= 0.69).

Figure 2 Univariable logistic regression adhesion-related bowel obstruction; OR Odds ratio, 95% CI OR 95% confidence interval of the odds ratio, p p-value.



Multivariable logistic regression for risk of adhesive bowel obstruction

In multivariable analysis, the lower gastrointestinal tract as the anatomical location of the index operation was the strongest independent risk factor for adhesive bowel obstruction (95% CI OR 1.71 – 12.22, p <0.01) (table 3). The severity of adhesions in the operative area was also an independent risk factor (95% CI OR 1.02 – 5.51, p 0.04). The number of previous laparotomies was not an independent risk factor.

Table 3 Multivariable logistic regression adhesion-related bowel obstruction; OR Odds ratio, 95% CI OR 95% confidence interval of the odds ratio, p p-value; Nagelkerke R2 0.15.

Patient factor	OR	95% CI OR		p
Number of previous laparotomies				
0	Ref			
1 or 2	0.60	0.23	1.55	0.29
≥3	1.89	0.68	5.29	0.23
Anatomical location index operation				
Other	Ref			
Lower GI	4.57	1.71	12.22	<0.01
Abdominal Wall	0.90	0.22	3.72	0.89
Zühlke score operative area				
No or mild adhesions	Ref			
Severe adhesions	2.37	1.02	5.51	0.04

Figure 3 and 4 show the cumulative risk over time for the occurrence of adhesive bowel obstruction stratified by the severity of adhesions and the anatomical location of the index operation (p <0.01 and p <0.01).

Figure 3 Cumulative risk over time for an episode of bowel obstruction stratified by the severity of adhesions during the index operation (p= <0.01). The dotted line represents severe adhesions, whereas the straight line represents no or mild adhesions.

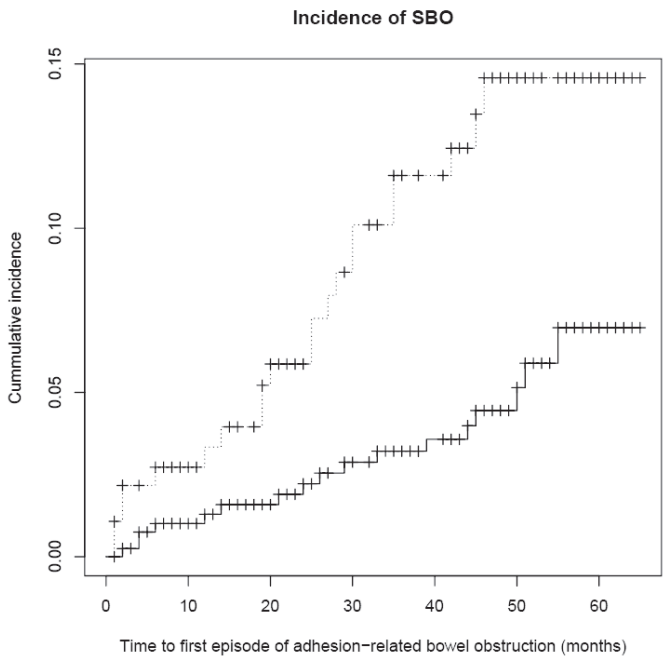
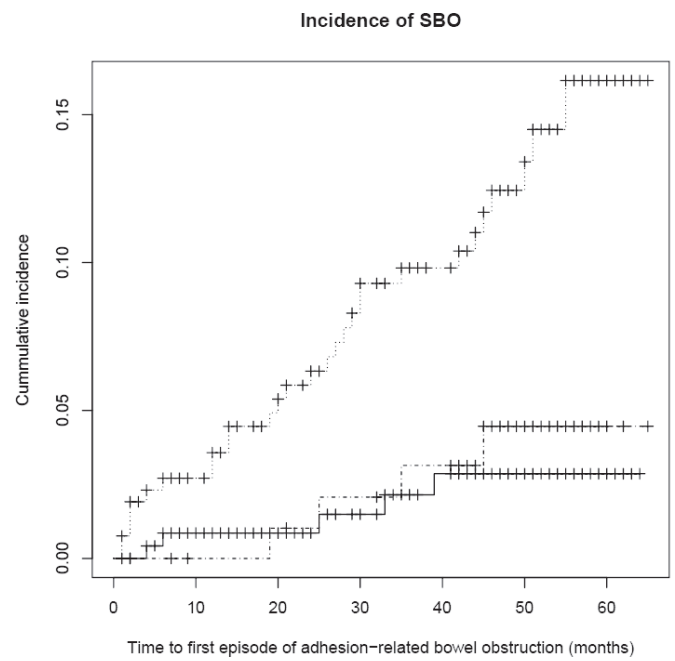


Figure 4 Cumulative risk over time for an episode of bowel obstruction stratified by the anatomical location of the index operation (p= <0.01). The dotted line represents the lower gastrointestinal tract, the dotted and dashed line represents the abdominal wall and the straight line other anatomical locations.



Discussion

About 6% of patients will develop an episode of adhesive bowel obstruction within 4 years following elective general abdominal surgery. Surgery on the lower gastrointestinal tract and severe adhesions at the index operation increase the risk for adhesive bowel obstruction by 5 and 3 times, respectively.

The incidence of adhesive bowel obstruction is higher than the 2.5% reported in the literature.[1] A likely explanation is the different data source. The reported incidence is mainly derived from registry based studies using (operative) coding systems, which are associated with reporting bias and might represent an underestimation of the total incidence.[7, 18] We might have slightly overestimated adhesions as the cause of small bowel obstruction by including patients who were managed conservatively and in whom adhesions as the cause for obstruction was strongly suspected in the absence of other causes. All cases of bowel obstruction were scrutinized to rule out other potential causes of bowel obstruction.[1] We chose to incorporate conservatively

managed cases because this reflects the complete morbidity of adhesive bowel obstruction and may elucidate important risk factors. In the Netherlands, patients have their medical data registered at a general practitioner's practice or a doctor at a nursing home when applicable. Furthermore, patients generally present their complaints at a general practitioner first, meaning that the medical history of the patient is complete and available. This type of healthcare organization improves the accuracy of data, even when obtained in a retrospective manner. A limitation of this study is the low absolute number of cases with adhesive bowel obstruction. Point estimates of the odds ratios of risk factors in regression analysis should therefore be interpreted with caution. Still, even with this low number of cases, the severity of adhesion at the index operation was found to be an independent risk factors for developing adhesive bowel obstruction.

This is the largest and most comprehensive cohort study, including intra-operative adhesion related factors. With an 88% completed follow-up of patients included in the LAPAD study and the low incidence of adhesive bowel obstruction, the attrition bias of this study is low, making it unlikely that missing outcome data would affect our results. The length of our follow-up period was sufficient for the majority of bowel obstructions to occur, although new cases of ASBO continue to develop for many years after surgery, previous studies have demonstrated that the majority of cases develop within the first 4 years.[9]

This study showed that the presence of severe adhesions increased the risk for adhesive bowel obstruction by two-fold and it significantly decreased the time to first episode of adhesive bowel obstruction. These results refute the relatively popular opinion that single strand of adhesions cause a higher risk for bowel obstruction than multiple tenacious adhesions. Possible explanation might be that due to more severe adhesions the bowel will be increasingly adhered to itself and to the abdominal wall, thereby compromising normal intra-abdominal bowel movement and increasing the chance of the occurrence of an obstruction. Surgery on the lower gastrointestinal tract, predominantly causes adhesion formation between the colon, small bowel, abdominal wall and, retroperitoneum. This might explain our finding that surgery on the lower gastrointestinal tract increases the risk for adhesive bowel obstruction by four times in comparison to other anatomical locations in the abdomen.[1, 8, 9] The negative impact of large peritoneal dissection in colorectal surgery is illustrated by the finding that a panproctocolectomy and total colectomy carry the highest risk for adhesion-related readmissions.[19] We did not find an association between intra-abdominal complications and an increased risk for adhesive bowel obstruction. This might be partially explained by the low incidence of intra-abdominal complications in our cohort. A study showed an increased incidence of small bowel obstruction after perforated appendicitis versus uncomplicated appendicitis. Although intra-abdominal complications may aggravate adhesion formation, severity of adhesions

due to increased peritoneal inflammation seems to only weakly relate to the clinical expression of adhesive bowel obstruction.[20, 21]

In a large clinical adhesion prevention trial the only factor significantly impacting the occurrence of adhesive small bowel obstruction was the usage of Seprafilm© at the index operation.[22] Due to its design, this trial was not suitable to assess risk factors for the main study endpoint. Additionally, the univariable risk analysis only assessed the episodes of adhesive small bowel obstruction that were treated surgically, which does not reflect the total incidence of adhesive small bowel obstruction as mentioned. Therefore the results of their analysis for factors impacting the occurrence of adhesive small bowel obstruction should be interpreted with caution.

We demonstrated that complete adhesiolysis does not decrease the risk for adhesive bowel obstruction. Scarce evidence suggests that due to the upregulation of proteins involved in peritoneal adhesion formation, adhesion reformation might be aggravated after adhesiolysis.[23, 24] Therefore, we advocate not to perform routine complete adhesiolysis during abdominal surgery, also because prolonged adhesiolysis is associated with increased risk of an iatrogenic enterotomy.[2] Our study showed that a history of multiple previous abdominal operations and more severe adhesions impact the occurrence of adhesive bowel obstruction, thus it might be advantageous to prevent adhesions from the first abdominal operation. Patients undergoing surgery on the lower gastrointestinal tract and patients with more severe adhesions after multiple previous operations should be counseled regarding an increased risk for adhesive bowel obstruction.

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Chapter 10

Animal models for preventing adhesion reformation: a systematic review and meta-analysis

Chema Strik[1], M.D., Kim E. Wever[2] PhD, Martijn W.J. Stommel[1], M.D., PhD,
Harry van Goor[1], M.D., PhD, FRCS, Richard P.G. ten Broek[1], M.D., PhD,
[1]Department of Surgery, [2]SYRCLE, Radboud University Medical Center, Nijmegen,
The Netherlands
Submitted

Abstract

Background: As many as 40- 66% of elective procedures in general surgery are reoperations. During reoperations, adhesions are often already present from previous operations and the need for adhesiolysis results in an increased operative time and a more complicated convalescence. During pre-clinical evaluation adhesion barriers are tested for their efficacy in preventing 'de novo' adhesion formation. It is unknown to which extent barriers are tested for prevention of adhesion reformation and which experimental models are most valid for translation into clinical efficacy. In this systematic review and meta-analysis we comprehensively assess the use of five commercial available adhesion barriers and laparoscopic adhesiolysis in preventing adhesion reformation in animal models.

Methods: Pubmed and EMBASE were searched for relevant studies. Included studies assessed peritoneal adhesion reformation not in the presence of an intra-peritoneal mesh after a standardized peritoneal injury and reported incidence of adhesions or an adhesion score as outcome. A modified scoring system was used to assess the methodological quality.

Results: 93 studies could be included. 84 studies assessed the efficacy of an adhesion barrier and 9 assessed surgical technique. No study met the criteria for low risk of bias. The pooled incidence of adhesions in the control groups was 90.99%. None of the commercially available adhesion barriers significantly reduces the incidence of adhesion reformation. Three commercially available adhesion barriers reduced the adhesion score of reformed adhesions, Seprafilm (SMD 1.38; $p < 0.01$), PEG (SMD 2.08; $p < 0.01$) and Icodextrin (SMD 1.85; $p < 0.01$). There is no difference between laparoscopic or open adhesiolysis with regard to the incidence of adhesion reformation or the adhesion score (RR 1.14; SMD 0.92; $p = > 0.05$)

Conclusions: Current commercially available adhesion barriers and laparoscopic adhesiolysis without using an adhesion barrier do not reduce the incidence of adhesion reformation in animal models. The methodological quality of animal models is poor and there is great heterogeneity with regard to the animal models used for assessing the efficacy of adhesion barriers.

Introduction

Postoperative adhesions form after abdominal surgery due to injured peritoneal surfaces and cause a life-long risk for small bowel obstruction, chronic pain, infertility and complications during reoperations.[1] Today, as many as 40- 66% of elective procedures in general surgery are reoperations.[2-4] During reoperations, adhesions are present from previous operations in about 90 percent and the need for adhesiolysis results in an increased operative time and a more complicated convalescence. The incidence of iatrogenic bowel injury during adhesiolysis is estimated at 6-10% and is associated with increased postoperative mortality and healthcare costs.[1, 4] Adhesion reformation is of particular clinical importance, the risk of iatrogenic bowel injury and more severe adhesions exponentially increases after multiple abdominal operations.[5, 6] Evidence suggests that the local expression of growth factors and proteins inhibiting fibrinolysis are increased in the peritoneum of patients with adhesions already present, potentially leading to aggravated adhesion reformation.[7, 8] As a result, adhesion barriers may be less efficacious in preventing adhesion reformation. This is supported by a clinical study in which icodextrin 4% had a non-significant reduction of the incidence of adhesion reformation from 95.7% at baseline to 68.7% at the second look operation whereas it did seem to prevent de novo adhesion formation.[9] A systematic review and meta-analysis demonstrated reduction of clinically relevant consequences of adhesions by hyaluronate carboxymethylcellulose and oxidised regenerated cellulose, however, included studies predominantly reported on prevention of 'de novo' adhesion formation or did not differentiate between patients with and without adhesions present at the index operation[10]. Awareness of reduced efficacy in preventing adhesion reformation compared to 'de novo' adhesion formation is low among surgeons.[11]

During pre-clinical evaluation adhesion barriers are tested for their efficacy in preventing 'de novo' adhesion formation. It is unknown to which extent barriers are tested for prevention of adhesion reformation and which experimental models are most valid for translation into clinical efficacy. In this systematic review and meta-analysis we comprehensively assess the use of five commercial available adhesion barriers and laparoscopic adhesiolysis in preventing adhesion reformation in animal models. Additionally, the impact of different study characteristics on the incidence of adhesion reformation and quality of adhesions was investigated to provide guidance for the design and the execution of future studies.

Methods

Search strategy, inclusion and exclusion criteria

In June 2017 electronic searches were performed in the Pubmed and Embase databases. The search strategies involved the following search components: "adhesion" and "peritoneum", "peritoneal adhesion", "animal", "prevention", "adhesiolysis", "anti-adhesive" and both the generic and trade names of known adhesion barriers.

We combined this with a search filter designed specifically to enhance the retrieval of animal studies.[12, 13] The complete search can be found in digital supplement 1.
The inclusion criteria and method of analysis were specified in advance in a protocol which is published on the website of SYRCLE. Studies were screened on the basis of title and abstract by two independent reviewers (CS and MS) in the webbased program EROS©. In case of doubt, the full paper was evaluated. Differences were discussed, and if necessary resolved with the help of a third person (RtB). Inclusion criteria were: the study assessed peritoneal adhesion reformation not in the presence of an intra-peritoneal mesh after a standardized peritoneal injury and addressed one of the following outcomes: incidence of adhesions or an adhesion score. Studies were excluded if it was not performed in animals or it was not an original full paper presenting original data. Chinese, Arabic and Cyrillic papers were excluded. If necessary, papers in languages other than English were translated.
Studies were excluded from the systematic review if there was no numerical or graphical data on any of the outcome measures, it used an intra-peritoneal mesh, was not an adhesion reformation model, the adhesion barrier was not applied intra-peritoneally or if the group of animals was not treated according to the same protocol. All studies were evaluated by two researchers independently from each other and any disagreements were discussed. Studies were excluded from the meta-analysis if there was no control group or no treatment group, if the group size was unknown, if the mean score was unknown or if there was no variance reported in the article.
The authors of articles with unreported data on relevant outcome measures or study details were contacted via e-mail. In case the authors did not respond, one follow-up e-mail was sent.

Study characteristics and data extraction

The following data were extracted from studies included in the systematic review: animal species (rat, rabbit, mouse, other), sex (male, female, mixed, unknown), number of animals in treatment and control groups, number of animals excluded or deceased, reason for exclusion, cause of death, type of model (cecal abrasion, uterine horn, other(for example ischemic button)), type of control group (internal or external), intervention used as control (no intervention, saline, placebo or a combination of these), perioperative treatment with analgesia, antibiotics or fluids for resuscitation, standardized peritoneal injury, timing of intervention (1st and 2nd or only at the 2nd operation), repeated injury at 2nd surgery, and the method of adhesiolysis (sharp and blunt, coagulation). Cecal abrasion as type of model comprised four variations: cecal abrasion alone, cecal abrasion plus sidewall damage, cecal abrasion plus ileal damage, and sidewall damage alone. We included the latter because cecum is regularly attached to the peritoneal sidewall area after damage. Bibliographic details such as author and year of publication were also registered.

We devised an 8-point scoring system to assess the methodological quality of included articles based on the tool published by Hooijmans et al..[14] Our methodological scoring system contained presence of an ethical statement, adequate allocation sequence generation, similar groups at baseline, blinded from treatment allocation, method of serosal injury specified and standardized, random outcome assessment, blinded outcome assessment and incomplete outcome data adequately addressed. Studies meeting 7 or 8 methodological criteria of risk of bias assessment were considered to have a low risk of bias.
Two outcome measures were assessed: incidence of adhesions and adhesion score. Type of scoring system (tenacity, extent, morphology, mixed) and the minimal and maximal value of the scoring system used were collected.

Data synthesis and statistical analyses

Data were analyzed using STATA 11.2, using the 'metan' package. Meta-analysis was performed for two outcome measures, the incidence of adhesions and adhesion score. The incidence of adhesions in the control groups was pooled using inverse variance. Additionally, the incidence of adhesions was computed by means of a risk ratio summary statistic and the adhesion score by computing the standardized mean difference (SMD) using Hedges' G. A random effects model was used to account for heterogeneity between the studies. Subgroup analyses were performed on both outcome measures and metaregression was used to assess significant differences between the subgroups. A minimum of 5 studies were required in each subgroup to perform an analysis. Subgroup analyses were performed for: animal species, gender, type of model, method of adhesiolysis, time interval between surgery, type of scoring system and repeated injury at 2nd laparotomy. The efficacy of commercial available barriers, oxidized regenerated cellulose, hyaluronate carboxymethylcellulose, icodextrin, polyethylene glycol and dextran, was assessed irrespective of the number of studies available for analysis. Additionally, the efficacy of saline for reducing the incidence of adhesions and the adhesion score was assessed.
When a study contained multiple control groups, the control group without an intervention was used. Additional positive control groups were analyzed as treatment groups. If a study contained multiple dosages or volumes of the same adhesion barrier, the most efficacious dosage or volume was chosen. If multiple treatment groups were compared with one control group the number of animals in the control group were divided by the number of treatment groups. When data were presented only graphically, we extracted numerical data from the graphs using ImageJ© digital image analysis software. In case the incidence in the control and treatment group was 100%, the incidence in both groups was reduced with 10% to facilitate meta-analysis. If standard error was reported this was converted to a standard deviation for meta-analysis. If the standard deviation was 0, the lowest standard deviation of

another group within that study was used to facilitate meta-analysis. In case a study contained separate protocols for multiple groups, these were analyzed as being separate studies.
Publication bias was assessed for the overall efficacy of adhesion barriers for the incidence of adhesions and adhesion score using a funnel plot with an Egger regression analysis.

Results

The search in PubMed and EMBASE yielded 6329 unique records of which 4555 could be excluded after checking the title and abstract. Out of 1774 studies, 93 (5%) studies assessed adhesion reformation and met our inclusion criteria, the other studies assessed de novo adhesion formation whether or not in the presence of an intra-peritoneal mesh (figure 1).

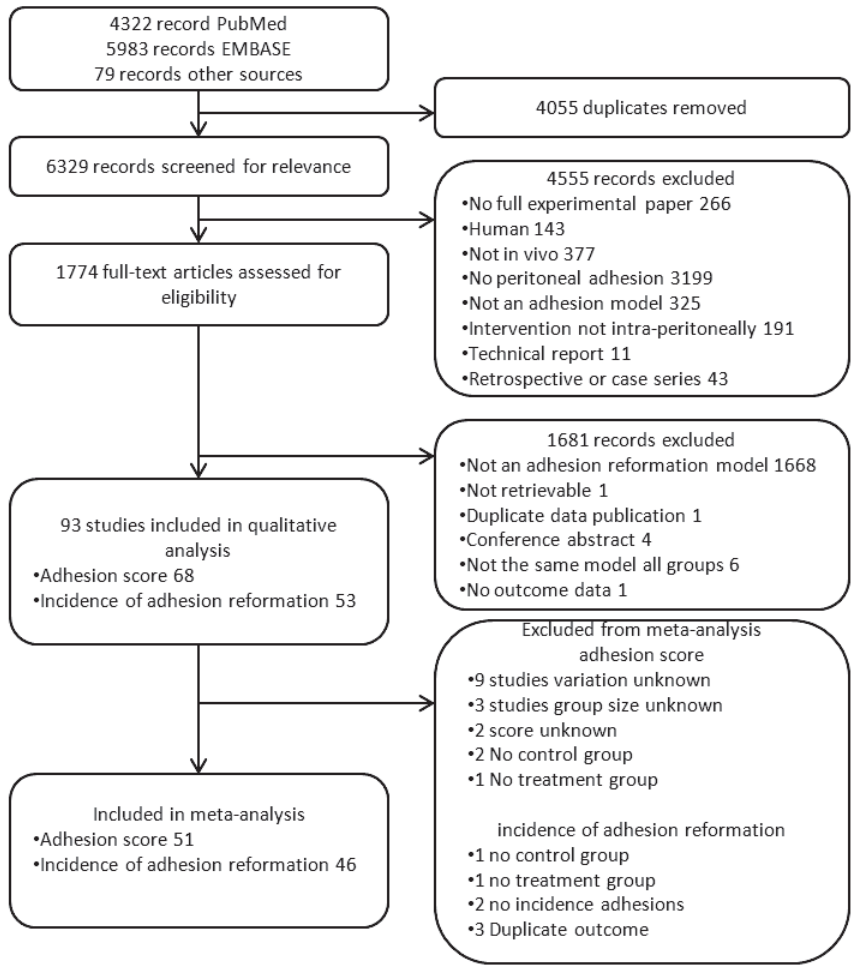
Characteristics of included studies

The characteristics of the 93 included studies are shown in figure 2. 84 studies assessed the efficacy of an adhesion barrier, whereas 9 studies assessed surgical technique. 53 (57%) studies used a cecal abrasion model, 34 (36%) an uterine horn model and 6 (7%) studies used other experimental models. From the 53 cecal abrasion models, 14 used a cecal abrasion only model, 8 a cecal abrasion plus ileal damage, 25 a cecal abrasion plus sidewall injury and 6 studies used a sidewall injury alone. Eleven (12%) studies applied an adhesion barrier at both surgeries. No study combined laparoscopic adhesiolysis with an adhesion barrier. 53 (57%) studies assessed the incidence of adhesions as outcome measure and 46 could be included in meta-analysis. 68 (73%) studies assessed an adhesion score as outcome measure and 51 (55%) could be included in meta-analysis.

Risk of bias

The risk of bias is shown in figure 3. No study met the criteria for low risk of bias. Therefore we could not perform a subgroup analysis for low risk of bias studies. Eight (9%) studies reported and used an adequate randomization method, 52 (56%) studies mentioned randomization but did not specify the method of randomization and 33 (35%) studies did not use an adequate randomization method. 55 (59%) studies adequately blinded outcome assessment, whereas 1 (1%) study did not specify blinding outcome assessment and 37 (40%) studies did not adequately blinded outcome assessment. 15 (16%) studies adequately blinded treatment allocation, in 76 (82%) studies it was not specified and in 2 (2%) studies it was not performed.

Figure 1 Flow-chart.



Incidence of adhesions in control groups and impact of study characteristics on outcome

The pooled incidence of adhesions in the control groups was 90.99% (Figure 4). Only one model did not develop any adhesions at all, this study (Luciano 1989 B) used a laparoscopic peritoneal sidewall abrasion model. The range of incidences of adhesions in control groups, excluding the study performed by Luciano 1989 B, was (60% to 100%).

Figure 2 General characteristics of the studies included in the systematic review: *Animal species*: 1 rabbit, 2 rat, 3 other, 4 not applicable (NA), 5 NA; *Sex*: 1 male, 2 female, 3 mixed, 4 unknown, 5 NA; *Type of experimental model*: 1 cecal abrasion, 2 uterine horn, 3 other, 4 NA, 5 NA; *Type of control group*: 1 external control, 2 internal control, 3 NA, 4 NA, 5 NA; *Intervention used in control group*: 1 no intervention, 2 saline, 3 placebo, 4 multiple control groups, 5 other adhesion barrier; *Time interval between 2nd operation and sacrifice*: 1 7 days, 2 14 days, 3 21 days, 4 other, 5 unknown; *Repeated peritoneal injury at second laparotomy*; 1 Yes, 2 No, 3 Unknown, 4 NA, 5 NA; *Method of adhesiolysis*: 1 blunt/sharp, 2 coagulation, 3 unknown, 4 NA, 5 NA; *Perioperative antibiotics, fluid resuscitation or analgesia*: 1 Yes, 2 No, 3 Unknown, 4 NA, 5 NA; *Type of scoring system*: 1 tenacity, 2 extent, 3 morphology, 4 combined, 5 other.

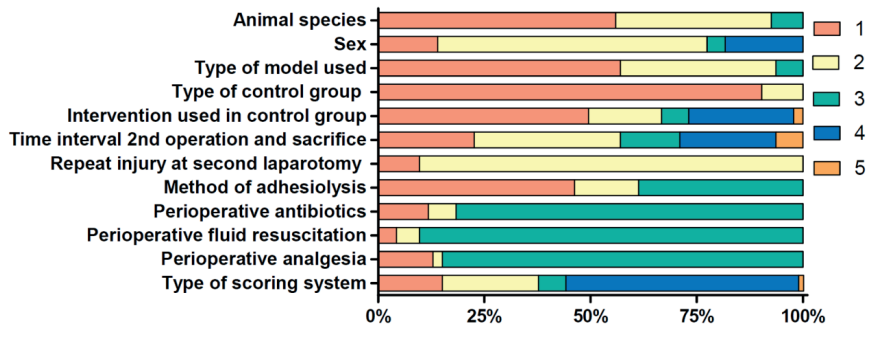


Figure 3 Risk of bias for the studies included in the systematic review showing the proportion of studies scoring low risk of bias (yes), high risk of bias (No) or did not specify (NS) the key methodological variables.

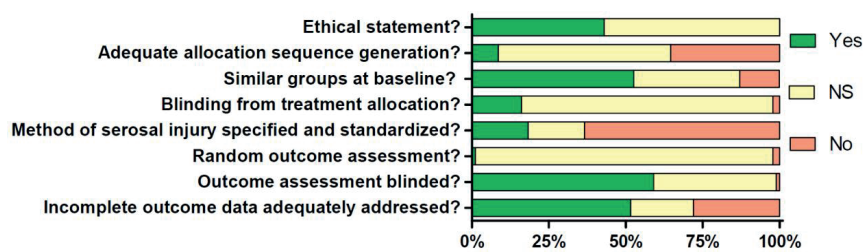
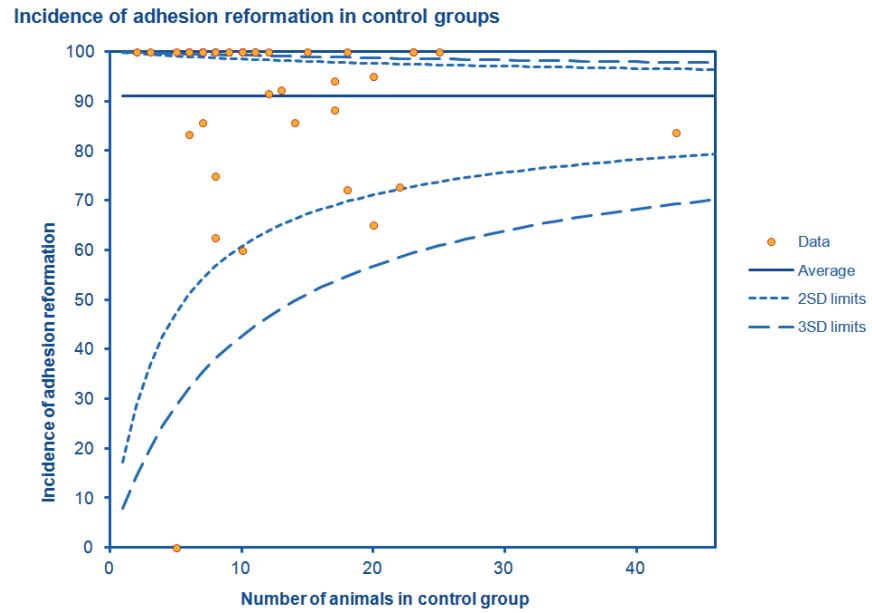


Figure 4 Funnel plot showing the incidence of adhesion reformation as a percentage of the total number of animals in the control group.



Subgroup analysis of the impact of experimental factors on the incidence of adhesion reformation showed significant heterogeneity between studies using rats (RR 0.88) and rabbits (RR 0.67; p =0.046). A trend was observed for significant heterogeneity between studies incorporating a repeated peritoneal injury (RR 0.62) or not (RR 0.84; p = 0.09). Type of model and gender showed no significant heterogeneity between studies (table 1).

Table 1 Subgroup analysis using meta-regression for assessing the impact of experimental factors on the incidence of adhesions, NS not specified, ‡ reference category, *not performed due to the low number of studies with this study characteristic.

Subgroup	Number of studies	Effect size	95% confidence interval		Heterogeneity	
			lower	upper	I² residual	p
Experimental model						
Cecal abrasion‡	31	0.80	0.73	0.87		
Uterine horn	7	0.90	0.69	1.12		
Other*	3					
Between subgroup					0.00	0.41
Animal species						
Rabbit	19	0.67	0.55	0.80		
Rat	16	0.88	0.80	0.97		
Other*‡	6					
Between subgroup					0.00	0.05
Gender						
Female‡	17	0.79	0.66	0.92		
Male	8	0.85	0.75	0.94		
Mixed*	3					
NS	13					
Between subgroup					0.00	0.21
Repeated peritoneal injury						
No‡	36	0.84	0.78	0.91		
Yes	5	0.62	0.37	0.86		
Between subgroups					0.00	0.09

Subgroup analysis of the impact of experimental factors on the adhesion score of reformed adhesions showed significant heterogeneity between studies using male (SMD 1.15) and female animals (SMD 2.05; p =0.03). The type of adhesion scoring system used showed a trend towards significant heterogeneity (p = 0.09). Type of model, species, repeated peritoneal injury and the time-interval between laparotomies showed no significant heterogeneity between studies (table 2).

A subgroup analysis of using an adhesion barriers at the first and second surgery could not be performed because only two studies with incidence and only four with adhesion score as outcome measurement were available.

Table 2 Subgroup analysis for the adhesion score, NS not specified, ‡ reference category, *not performed due to the low number of studies with this study characteristic or because subgroup is not specified.

Subgroup	Number of studies	Effect size	95% confidence interval		Heterogeneity	
			lower	upper	I² residual	p
Experimental model						
Cecal abrasion	25	1.66	1.24	2.08		
Uterine horn‡	19	2.01	1.51	2.51		
Other*	2					
Between subgroup					70.43	0.45
Animal species						
Rabbit	25	1.87	1.44	2.31		
Rat	15	1.99	1.42	2.56		
Other*‡	6					
Between subgroup					68.09	0.56
Gender						
Female‡	29	2.05	1.68	2.42		
Male	6	1.15	0.40	1.91		
Mixed*	3					
NS*	8					
Between subgroup					63.46	0.03
Repeated peritoneal injury						
No‡	38	1.81	1.47	2.16		
Yes	8	1.91	1.10	2.71		
Between subgroups					70.48	0.84
Time between surgery						
7 days	12	2.21	1.58	2.83		
14 days	17	1.53	1.03	2.03		
21 days	6	2.02	1.20	2.84		
Other*‡	11					
Between subgroups					67.16	0.30
Method adhesiolysis						
Blunt and sharp	20	1.77	1.28	2.27		
Coagulation	7	1.87	1.02	2.72		
NS*	19					
Between subgroups					70.22	0.96
Type of adhesion scoring system						
Tenacity‡	10	1.40	0.76	2.05		
Extent	16	2.15	1.63	2.67		
Combination	18	1.63	1.16	2.10		
Other*	2					
Between subgroups					65.04	0.09

Efficacy of adhesion barriers

Adhesion barriers, when pooling all studies (including commercially available and experimental barriers), reduce the incidence of adhesion reformation (Risk Ratio 1.35; 95% CI 1.21 – 1.50; p <0.01) and the adhesion score of reformed adhesions (SMD 1.94; 95% CI 1.61 – 2.27; p <0.01). The forest plots are shown in supplement 1 and 2. When analyzed separately, none of the commercially available adhesion barriers reduces the incidence of adhesion reformation (figure 5). Three studies assessed the efficacy of Seprafilm (RR 0.90; p 0.24), 5 studies assessed Oxidized Regenerated Cellulose (ORC; RR 0.80; p 0.49), 2 studies assessed PEG (RR 0.85; p 0.09), 4 studies assessed Dextran (RR 0.99; p 0.30) and 1 study assessed the efficacy of Icodextrin (RR 0.56; p 0.06). Saline (RR 0.98; p 0.59) did not reduce the incidence of adhesion reformation.

In contrast to reduction of incidence, three commercially available adhesion barriers individually reduced the adhesion score of reformed adhesions (figure 6). Three studies

Figure 5 Forest plot showing the efficacy of commercially available adhesion barriers in reducing the incidence of adhesion reformation.

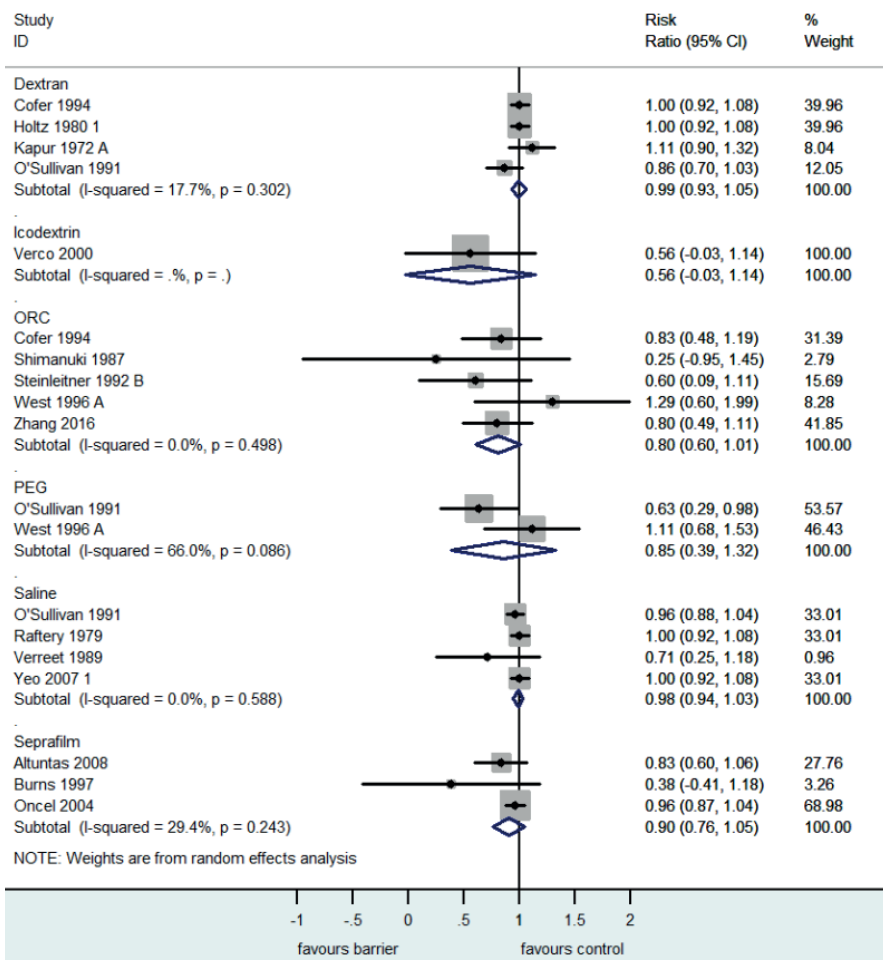
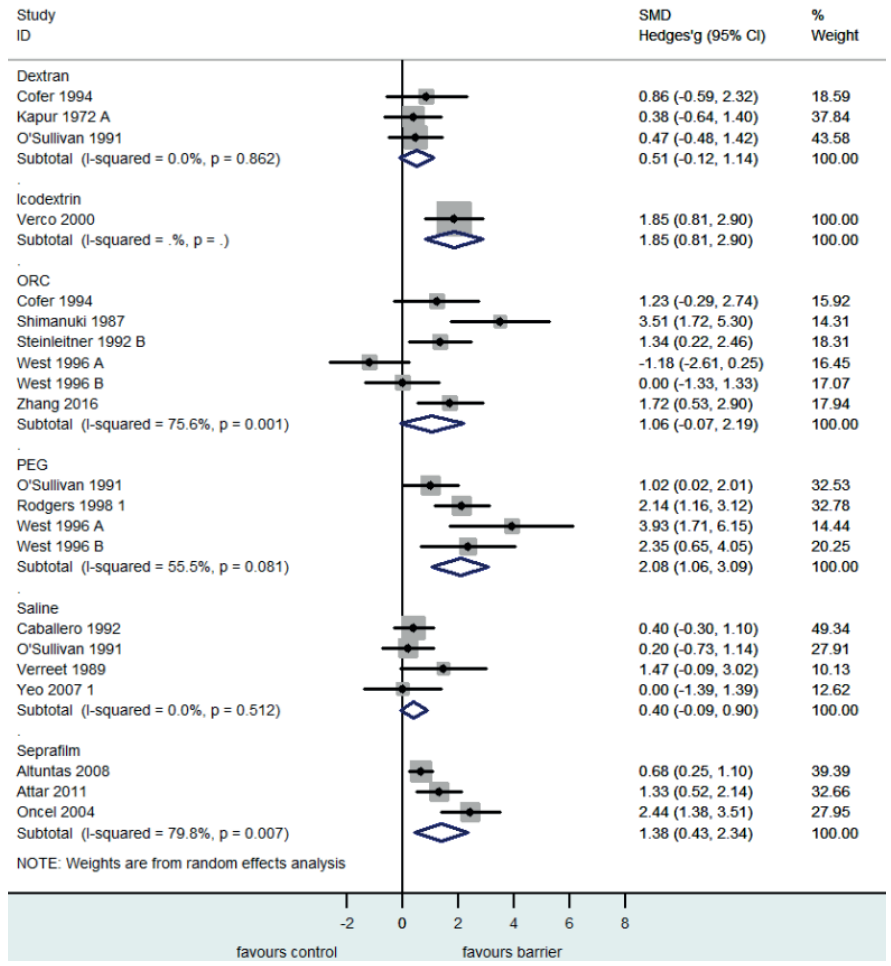


Figure 6 Forest plot showing the efficacy of commercially available adhesion barriers in reducing the adhesion score of reformed adhesions.



assessed the efficacy of Seprafilm (SMD 1.38; p <0.01), 4 studies assessed the efficacy of PEG (SMD 2.08; p <0.01), 1 study assessed the efficacy of Icodextrin (SMD 1.85; p <0.01). Three studies assessed the efficacy of Dextran (SMD 0.51; p 0.11), and 6 studies assessed the efficacy of ORC (SMD 1.06; p 0.07), and did not significantly reduce the adhesion score of reformed adhesions. Saline (SMD 0.40; p 0.51) did not significantly reduce the adhesion score of reformed adhesions.

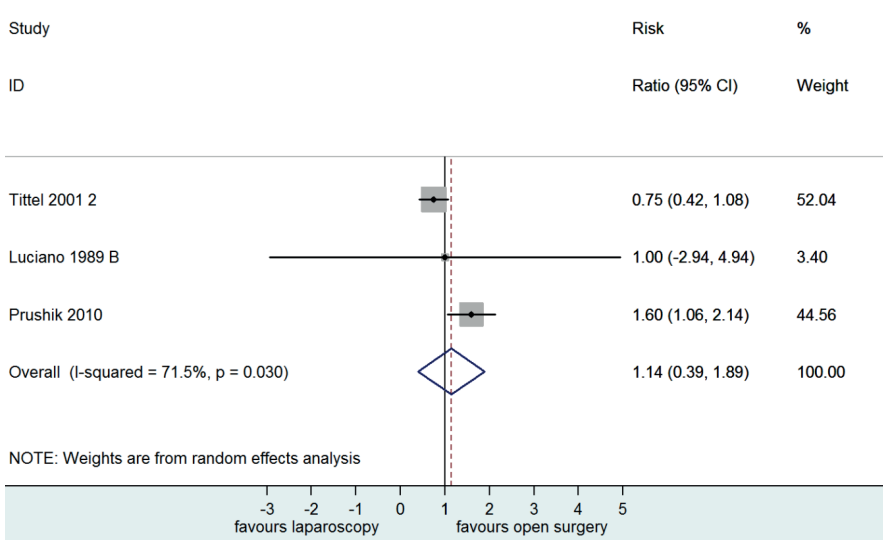
Publication bias of studies assessing the efficacy of adhesion barriers

Analysis of the funnel plot was performed for the overall efficacy of adhesion barriers in reducing the incidence of adhesions and in reducing the adhesion score. The egger's regression analysis showed no significant evidence for publication bias in both outcome measures (incidence of adhesions p = 0.18; adhesion score: p = 0.50). Trim and fill analysis did not indicate any missed data points.

Efficacy of surgical technique

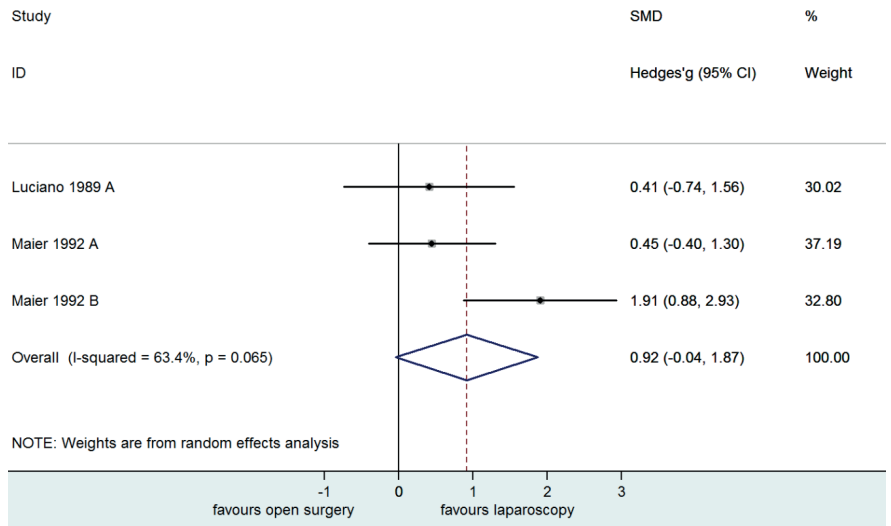
Seven out of 9 studies that assessed surgical technique compared the efficacy of laparoscopic versus open adhesiolysis. Three studies used the incidence of adhesion reformation and 4 studies used an adhesion score as outcome measure. Two studies assessed the efficacy of CO2 or Nd:YAG laser versus electro microsurgery (data not pooled).

Figure 7 Forest plot showing the efficacy of laparoscopic versus open adhesiolysis in reducing the incidence of adhesion reformation.



There was no difference between laparoscopic or open adhesiolysis with regard to the incidence of adhesion reformation (RR 1.14; figure 7).
A trend was seen toward a reduced adhesion score in favor of laparoscopic adhesiolysis (SMD 0.92; p 0.07; figure 8). Publication bias was not assessed due to the limited number of studies available for analysis.

Figure 8 Forest plot showing the efficacy of laparoscopic versus open adhesiolysis in reducing the adhesion score of reformed adhesions.



Discussion

Concise statement of principal findings

The results of this systematic review and meta-analysis show that none of the commercially available adhesion barriers reduces the incidence of adhesion reformation, however, reduce the severity of reformed adhesions in animal studies. There is no evidence regarding the efficacy of laparoscopic adhesiolysis in reducing the incidence of adhesion reformation. Only 5% of all animal studies on adhesion prevention assessed the efficacy of adhesion barriers or surgical technique for the prevention of adhesion reformation. Studies were highly heterogeneous with regard to the employed study characteristics, and overall methodological quality was poor.

Strengths and limitations of the present study

We were able to include a large number of studies per outcome measure, which enabled us to investigate the effect of several experimental factors. The studies included in our systematic review and meta-analysis were highly heterogeneous. We have accounted for this heterogeneity by using a random effects model and performing subgroup analysis, however, differences between subgroups should be interpreted with caution because some subgroups represent only few studies and a limited number of animals. The included studies may be subject to publication bias. Although the Egger's regression and trim and fill analysis did not observe any significant publication bias, the included studies all reported that at least one of the adhesion barriers tested is effective in reducing the score of reformed adhesions. An explanation that at least one adhesion barrier was effective could be the differences in methodological quality, heterogeneity or only publication of positive results.[15] Importantly, this could lead to an overestimation of the effect sizes of the efficacy of adhesion barriers. Despite the potential overestimation none of the commercially available adhesion barriers reduced the incidence of adhesion reformation in individual analysis.

Comparison to other studies and clinical implications

The overall methodological quality was low as no studies met the criteria for low-risk of bias and reporting was poor. A recent systematic review demonstrated that this is the case for many animal studies in different medical fields.[16] The method of randomization and blinding of treatment allocation was not specified in 56% and 82% of the studies included in this systematic review. This underlines an important aspect, namely, the suboptimal reporting of key characteristics central to good scientific practice. One study demonstrated that the demands from nine different journals, selected on the basis that they publish a high number of animal studies, for the description of animal studies are limited in a way that studies cannot adequately repeated.[17] It is of great importance that the methodology and reporting of animal studies improve in order to increase the reproducibility and ultimately the translational value of animal studies to clinical practice.

The commercially available adhesion barriers did not significantly reduce the incidence of adhesion reformation. 93 out of 1774 studies assessed the efficacy of adhesion barriers or surgical technique on adhesion reformation and only eleven studies assessed commercially available barriers with icodextrin being the most poorly studied with one study assessing its efficacy. Considering the rate of 40 to 66% of reoperations in elective abdominal surgery and the large clinical burden of adhesiolysis, the number of animal studies assessing adhesion reformation is low.[2-4] In a national survey regarding the awareness of adhesions, almost 80% of the surgeons that have used adhesion barriers did so during reoperations for adhesion-related complications. Seprafilm® and Adept® (Icodextrin) were the most used adhesion barriers.[11] The indications for using Seprafilm® as described by the manufacturer do not differentiate between preventing 'de novo' adhesions or reformed adhesions whereas the indication for using Adept® is limited to preventing adhesion reformation in gynecological laparoscopic adhesiolysis and is contra-indicated in patients requiring a laparotomy incision, bowel resection, appendectomy or that have peritonitis.[18, 19] The efficacy of Adept in reducing the incidence of adhesion reformation after laparoscopic adhesiolysis in gynecologic surgery is questionable and there is no evidence for the effectiveness of Adept in general surgery, which findings compare with our animal data.[10, 20, 21] Prevention of adhesion reformation is key in reducing the clinical burden of adhesions and both experimental animal and clinical evidence is lacking in how to optimally prevent adhesion reformation by adhesion barriers.

Laparoscopic adhesiolysis did not significantly reduce the incidence of adhesion reformation in the included animal studies. In 3 studies assessing the incidence of adhesion reformation there was a minimal difference between open and laparoscopic adhesiolysis (RR 1.06). It has been reported that the incidence of de novo adhesion formation against the incision is reduced after laparoscopic surgery in comparison to open surgery and that laparoscopic surgery is associated with a reduced incidence of adhesive small bowel obstruction.[1, 22] A similar efficacy might not apply to adhesion reformation after adhesiolysis. Laparoscopic adhesiolysis as intended operative procedure is limited to improving fertility of women with peri-adnexal adhesions and treating chronic abdominal pain related to abdominal adhesions.[23, 24] Our animal data indicate that laparoscopic adhesiolysis alone is not effective in reducing the incidence of adhesion reformation, and could benefit from usage of an adhesion barrier as adjuvant to improve efficacy in reducing adhesion reformation.

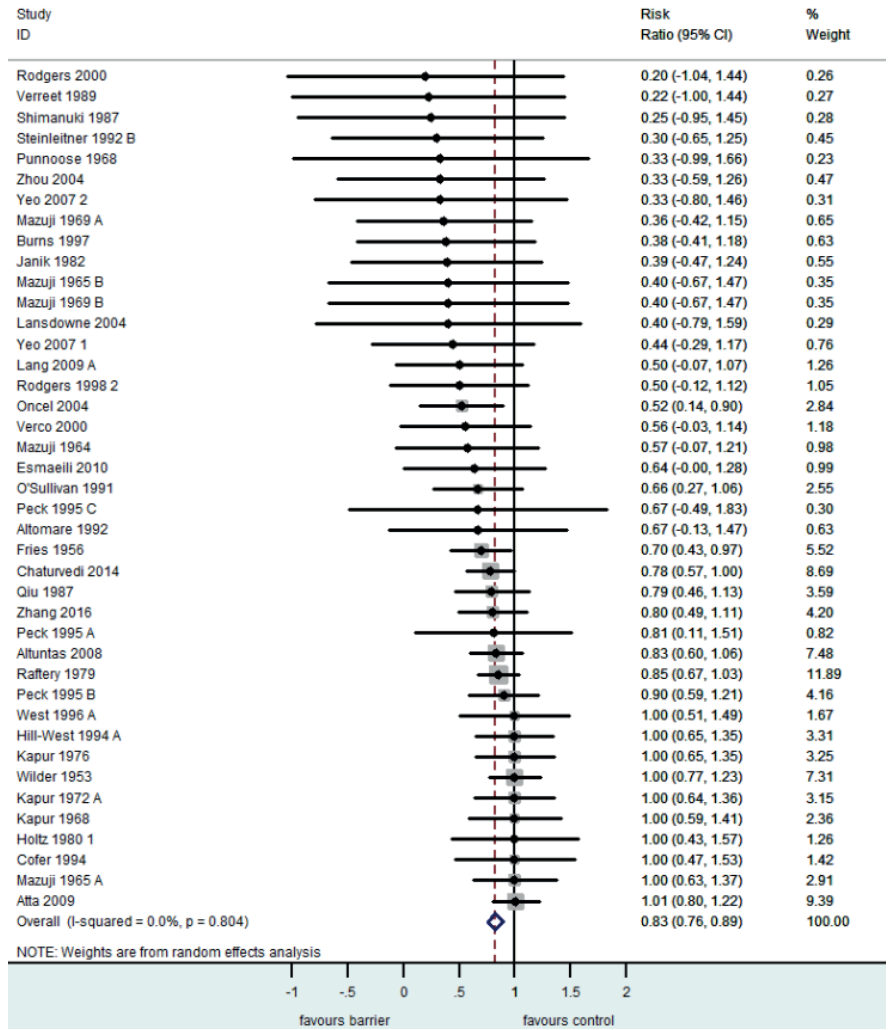
We have found that the type of gender and animal used significantly impact adhesion reformation. We advocate that future studies should use mixed gender populations. When interpreting the results of animal studies assessing the efficacy of adhesion barriers, the large effect sizes in rabbits compared to rats should be taken into account. Possibly heterogeneity and predominant use of the uterine horn model in rabbits explain the difference. Unfortunately due to small subgroup size we were not able to further analyze the impact of covariates regarding animal species. Studies incorporating a repeated peritoneal injury showed a trend towards a lower effect size when assessing the incidence of adhesion reformation. We propose using a repeated peritoneal injury model because most reoperations in humans involves peritoneal dissection and subsequent damage.[25] The high heterogeneity of the included studies is reflected in the wide range of 60-100% in the incidence of adhesion reformation in control groups. It has been recognized that animal studies assessing the efficacy of adhesion barriers are highly heterogeneous and efforts have been

made to improve the standardization of animal models by comparing several models of adhesion formation.[26] However, this has not led to a experimental model employed by different study groups. Only 53 of 93 studies incorporated the incidence of adhesion reformation as an endpoint of the study. This is a relatively low number as only the absence of adhesions will preclude complications secondary to adhesiolysis, adhesive bowel obstruction and female infertility. To increase translational value, the primary endpoint of animal studies assessing the efficacy of adhesion barriers should be the overall incidence of adhesions. We have found a pooled incidence of 91% with a range of 60-100% in controls which can be used for power calculations of future studies. Almost all studies employed a different method to score adhesions and the method of scoring adhesions showed a trend towards a larger effect size when only extent was assessed in comparison to a score based on the tenacity or a combination of tenacity and extent. It has been tried to standardize the method of scoring adhesions, however this has not gained wide application.[27] Adhesion scores should only be incorporated as secondary endpoints and if scored, the tenacity of adhesions is particularly important as more tenacious adhesions correlates with iatrogenic organ injury during adhesiolysis.[4, 28] Systematic reviews and meta-analysis of animal studies have shown to be a useful tool in improving the design of future animal studies as well as an aid in the translation of animal studies to clinical trials.[29, 30] Our study provides several recommendations for improving experimental studies. Future animal studies testing new anti-adhesive agents should include both de novo adhesion prevention and adhesion reformation, use the most challenging model e.g. repeated peritoneal injury model, and use adhesion incidence as primary outcome. Furthermore, when designing a clinical study of adhesion prevention with barriers, patients with baseline adhesions should be analyzed separately in order to increase the clarity of results.

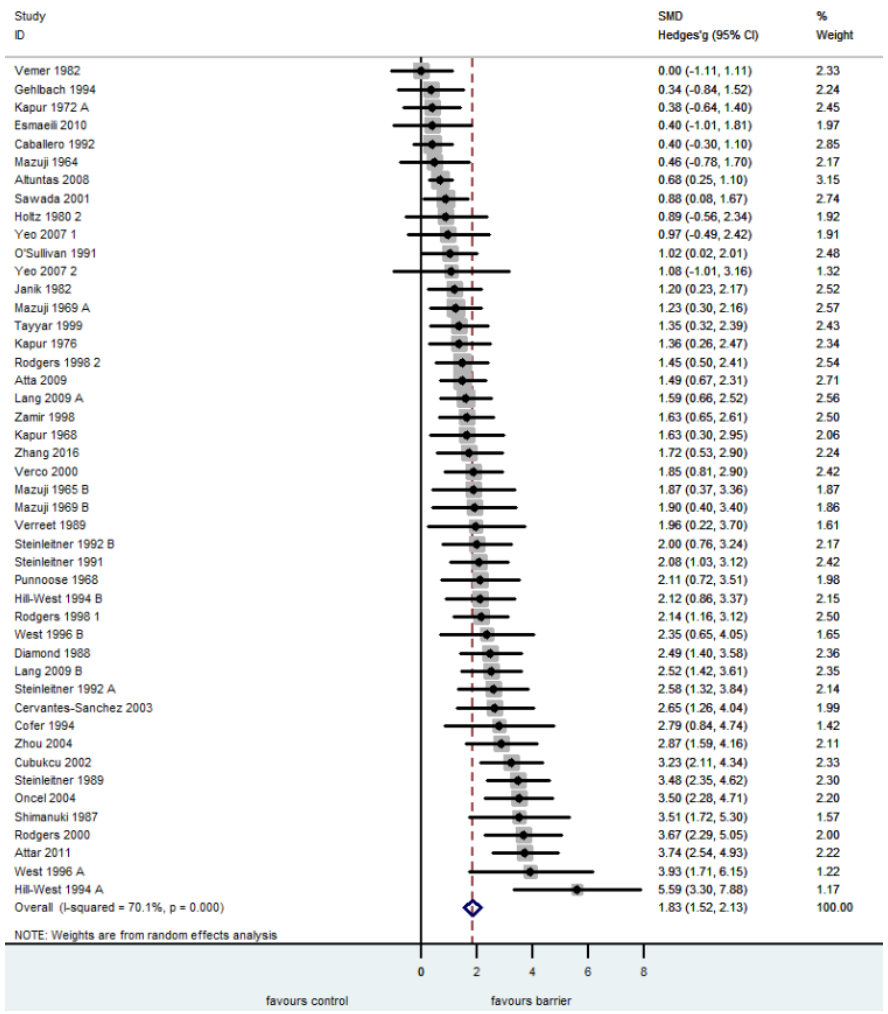
Conclusion

Current commercially available adhesion barriers and laparoscopic adhesiolysis without using an adhesion barrier do not reduce the incidence of adhesion reformation in animal models. Overall, the methodological quality of animal models is poor and there is heterogeneity with regard to the animal models used for assessing the efficacy of adhesion barriers. The results of this systematic review and meta-analysis can be used to aid in the improvement of the design of animal and clinical studies assessing adhesion-related outcomes.

Supplement 1 Pooled analysis of the efficacy of the different adhesion barriers in preventing adhesion reformation.



Supplement 2 Pooled analysis of the efficacy of adhesion barriers in reducing the score of adhesion reformation.



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Chapter 11

General discussion

Consequences of adhesiolysis during general abdominal surgery

Three studies in this thesis address the impact of adhesions and adhesiolysis on clinical morbidity and its associated costs, quality of life, functional status, ~~chronic post-surgical pain~~ and gastro-intestinal complaints. All three studies utilize data from the prospective LAPAD (LAParotomy or LAParoscopy and ADhesiolysis) study population.[1] The strength of these studies lies within the reliability and completeness of detailed information on pre-operative clinical data, postoperative complications and costs. During surgery, specific surgical data including adhesions and adhesiolysis was collected through direct observation by a trained researcher. Additionally, patients undergoing various types of abdominal surgery (upper gastrointestinal (GI), hepato-pancreatico-biliary (HPB), colorectal, hernia and vascular surgery) were included obtaining a broad picture of adhesiolysis related sequelae. A limitation of these studies is that the cohort is recruited from a single Dutch tertiary referral centre and therefore the results should be interpreted with caution regarding their generalizability to non-academic hospitals and other countries where the healthcare system significantly differs from the Dutch system. Another limitation is the small number of patients who underwent laparoscopic surgery. In the last decade the number of minimally invasive procedures increased almost exponentially and, for example, laparoscopic resection of colorectal cancer is standard of care in most western countries.[2, 3] However, a large proportion of patients in the LAPAD database that was operated via an open approach, would also not be routinely operated by laparoscopic approach nowadays (e.g. complex ventral hernia surgery).

The LAPAD study demonstrates that adhesiolysis requires a median of 20 minutes operative time and is associated with a 10% risk of an iatrogenic enterotomy. Patients requiring adhesiolysis have an increased incidence of sepsis, intra-abdominal complications, wound infections, longer hospital stay and higher mean hospital costs of about 4500 $ per admission. Patients with an iatrogenic enterotomy have a significantly increased risk for mortality. Clavien-Dindo grade 4 complications, readmissions and chronic abdominal pain showed to have the largest negative impact on functional status and quality of life. Additionally, one in three patients will have Chronic Postoperative Abdominal Pain (CPAP) and 9 out of 10 patients reported to have gastrointestinal complaints. The LAPAD study clearly demonstrates the significant clinical and socioeconomical burden of adhesiolysis, with impact on healthcare in and outside the hospital. In some hospitals already 40 to 66% of elective abdominal procedures in general surgery are reoperations and this percentage will increase due to a higher life expectancy and advances in surgical technology and anaesthesiology.[4-7] Our consistent results in the various domains of disease burden of adhesiolysis shifts the focus of adhesion research of bowel obstruction and female secondary infertility to adhesiolysis as the most relevant adhesion-related complication.

Our studies provide key data for proper patient counselling and decision making before surgery. Less than 10% of surgeons and gynaecologists routinely inform their patients about the risks of adhesions and adhesiolysis during informed consent.[8-10] Awareness of the impact of adhesiolysis and CPAP should affect decision making for surgery, especially in elderly patients and in cases where alternatives for surgery are present. The importance of addressing quality of life and functional status is supported by studies in oncologic patients which show improved patient satisfaction, detection of unrecognized problems, better health outcomes and changes in therapeutic management in some cases.[11, 12]

Risk for adhesion-related complications

There is a lack of progress in implementing adhesion prevention by medical professionals and policy makers due to the lack of awareness regarding the negative impact adhesions have on patients and society. Studies show that the incidence of adhesion-related complications is frequently underestimated by surgeons and gynaecologists.[8-10] Questions remain regarding the optimal strategy for using adhesion barriers to reduce clinically relevant outcomes. The second part of this thesis determined risk factors for adhesion-related complications in order to aid in improving patient selection that would benefit the most from adhesion barriers.

All four studies used the prospective data of the LAPAD study to assess risk factors for prolonged and difficult adhesiolysis, iatrogenic enterotomy, future repeat surgery and adhesive bowel obstruction ~~respectively~~. A limitation is the relatively small study population for the number of risk factors that have been assessed and the number of patients who developed the outcome of interest. Thus, our results require validation in a large cohort including a greater proportion of patients undergoing laparoscopic surgery and patients from different types of hospitals. Two important developments in quantifying data on complications, the Classification of Intraoperative Complications (CLASSIC) for intra-operative and the Clavien-Dindo classification for post-operative complications, should aid in improved reporting.[13, 14] An important drawback of both classifications is that they lack data on the aetiology of complications, which makes it difficult to establish causality and to develop targeted interventions for prevention or improvement. “Big data”, a term used for datasets whose size, complexity and dynamic nature impose significant problems for traditional statistical methods, could be a next step in identifying patients at risk for adhesion-related complications. Large observational datasets are well suited for developing predictive models and tools for analysing the data are becoming better useable and more sophisticated.[15] An example is the training of IBM’s Watson by oncologists from the Memorial Sloan- Kettering Cancer Center in aiding physicians in optimizing decision-making for patients with lung cancer.[16, 17] A dataset using observational data on a regional or national level that incorporates detailed patient- and disease-specific as well as peri-operative information could lead to improved patient selection for using adhesion barriers.

The combined results of our four studies show that the number of previous laparotomies, a history or presence of an intra-peritoneal mesh, the requirement of a complete midline incision, surgery involving the lower gastro-intestinal tract, abdominal wall surgery and hepatic resections due to malignancy, young age and female sex are important risk factors for adhesion-related complications. Selecting a surgical population at risk before their first operation instead of using adhesion barriers after all laparotomies or laparoscopies may aid in more tailored adhesion prevention and improve cost-effectiveness. An additional argument to use an adhesion barrier at the first operation is the concern that adhesion barriers are less efficacious in preventing adhesion reformation. Adhesiolysis combined with icodextrin 4% had a non-significant reduction of the incidence of adhesion reformation from 95.7% at baseline to 68.7% at the second look operation whereas it did prevent de novo adhesion formation in laparoscopic gynaecological surgery.[18] Reduced efficacy in reoperations might explain some of the failures of anti-adhesive barriers in clinical trials that seemed successful in pre-clinical evaluation. Current commercially available adhesion barriers and laparoscopic adhesiolysis without using an adhesion barrier do not reduce the incidence of adhesion reformation in the few animal studies performed on this subject. Animal models of adhesion reformation are an indispensable asset in the development of new barriers, which should be recognized by regulatory authorities and all manufacturers that develop anti-adhesive agents.

In the systematic review “Benefits and harms of adhesion barriers for abdominal surgery” clinical efficacy of adhesion barriers was demonstrated with level 1a evidence.[19] The studies, however, did not differentiate between patients with and without adhesions present at the index operation, and thus the efficacy of adhesion barriers was potentially underestimated. Unfortunately, this landmark study has not led to routine usage of adhesion barriers in abdominal surgery. Doubts about the need for adhesion prevention in the laparoscopic era and the perceived high costs of adhesion barriers are two important issues why adhesion barriers are seldom used.[8, 9] A recent prospective multi-centre observational study comparing the incidence of adhesion formation after open or laparoscopic colorectal surgery showed that laparoscopic colorectal cancer resection is associated with a lower incidence of adhesions to parietal surfaces but not of visceral adhesions.[20] This finding combined with epidemiological data regarding adhesion-related complications after laparoscopy plea for adhesion prevention in laparoscopic surgery. The use of adhesive barriers in open colorectal surgery was found to be cost-effective in preventing adhesion-related complications and associated with low costs (135 US dollars per patient) in laparoscopic colorectal surgery in a modelling study from our group (Stommel et al, submitted for publication). Notably, chronic pain was not incorporated in this analysis. The costs of chronic postoperative pain associated with adhesions is difficult to measure due to uncertain causality and the multi-disciplinary treatment

patients receive over a prolonged period of time.[21] Due to the low incidence of colorectal surgery in young fertile women, infertility was excluded from the analysis as well. However, secondary infertility inflicts a huge financial burden for patients; 20% of an individual's disposable income is required to pay for fertility treatment in most European countries.[22] Even when infertility and chronic postoperative pain are excluded, the incremental cost-effectiveness ratio for adhesion prevention is comparable to treating hypertension in order to reduce secondary complications, a disease for which treatment has gained worldwide acceptance for several decades.[23]

Future perspectives

The agenda of future research and developments in preventing the morbidity associated with peritoneal adhesions is depicted in Figure 1. The five most important goals for patients requiring abdominal surgery are:

1. Reducing the incidence of chronic postoperative abdominal pain associated with adhesions
2. Reducing iatrogenic organ injury during adhesiolysis
3. Reducing adhesive bowel obstruction
4. Reducing infertility caused by adhesions
5. Increasing the quality of life of patients potentially subjected to problems of peritoneal adhesions

Figure 1 Adhesion 2.0 sustainable goals.

Concerted action is required from surgical specialists operating in the abdomen and pelvis, healthcare workers engaged in the peri-operative care of surgical procedures, hospital managers, insurance companies, policy makers and patients to improve clinical outcomes of adhesion-related complications. The focus should lie on value based healthcare taking into account patient reported outcomes and action should be undertaken to inform patients who will undergo abdominal surgery about their long term risk of adhesion-related complications. We started Delphi rounds to develop a clinical adhesion score which takes into account the four most relevant clinical problems of adhesions: adhesiolysis related complications, small bowel obstruction, female secondary infertility and chronic abdominal pain. The goal is to obtain uniformly defined clinically relevant outcomes for future research on peritoneal adhesions and adhesiolysis. Assessing outcomes critical for clinical decision making is challenging because complications from adhesions and adhesiolysis are diverse, and require long-term follow-up.

Additionally, we are exploring a clinical diagnostic and therapeutic pathway by incorporating cineMRI, shared decision making and appropriate use of an adhesive barrier for chronic abdominal pain associated with adhesions. Improvement of imaging adhesions in the abdomen and pelvis away from the abdominal wall is studied with automatic computer analytic programs using images from cineMRI scans and first results are encouraging (Randall et al, accepted for publication in the British Journal of Radiology). Hopefully, this will make non-invasive detection of adhesions less operator and patient dependent and will improve patient selection for treatment decision in chronic abdominal pain.

Improved efficacy in preventing adhesion reformation and usability during laparoscopic surgery is key to the development of new barriers. However, preventing adhesion formation at the initial abdominal operation, either performed open or laparoscopically, is the most important step to reduce the incidence of adhesion-related complications.

This thesis adds substantial data to an evidence based guideline on peritoneal adhesions and adhesion prevention for general and gynaecological surgery. This guideline has recently been developed and is currently reviewed by members of the Dutch Adhesion Group. Broad acceptance and implementation of this guideline will reduce the disease burden of peritoneal adhesions for patients undergoing abdominal and pelvic surgery.

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Chapter 12

Summary

Introduction

Since the 'SCAR study group' published its first landmark paper in 1999, demonstrating that adhesion formation is the most common cause of long-term complications after abdominal surgery, scientific interest in adhesion formation and adhesion prevention increased.[1-4] The recent publication of the systematic review and meta-analysis 'The burden of adhesions in abdominal and pelvic surgery' from our group demonstrated, in a complete and concise manner, the large negative impact of adhesions and the four most important complications of peritoneal adhesions (small bowel obstruction, difficulties at repeat abdominal surgery, female infertility and chronic pain) on clinical and socio-economic outcomes.[5] Progress in improving adhesion prevention from medical professionals and policy makers has been stalled, probably due to the lack of awareness regarding the negative impact adhesions have on patients and society. Studies show that the incidence of adhesion-related complications is frequently underestimated by surgeons and gynaecologists and that less than 10% routinely inform their patients about the risks of adhesions during informed consent.[6-8] This thesis aims to improve the knowledge regarding the impact of peritoneal adhesions and adhesiolysis on postoperative outcomes and to investigate risk factors for adhesion-related complications.

Chapter 1 provides an introduction and outline of this thesis

Chapter 2 gives a comprehensive overview of the current knowledge regarding the inflammatory response of the peritoneum on various pathological triggers, such as surgical trauma, invasive pathogens and tumour. All mentioned triggers can be involved in abdominal surgery. Regardless of the type of injury to the peritoneal mesothelial cells, an inflammatory response is activated attempting to heal the peritoneal surfaces. The peritoneal response comprises four interacting pathways, an immunological, a humoral, a coagulation and a neurogenic pathway. Fibrous tissue connecting organs, surfaces and structures is commonly the ultimate result.

Our group demonstrated in 2000 in a retrospective series of 270 repeat intraperitoneal operations that an iatrogenic enterotomy occurred in 19% of patients and that these patients had significantly more postoperative complications and relaparotomies compared to those without an enterotomy.[9] With these results in mind, the LAParotomy or LAParoscopy and ADhesiolysis (LAPAD) study was performed, which results are described in **Chapter 3**. The LAPAD study is a prospective cohort study designed to assess data on adhesiolysis and inadvertent organ injury that were gathered by direct observation during the operation. A total of 755 surgeries in 715 patients were included. Adhesiolysis was required in 475 (62.9%) operations. Median adhesiolysis time was 20 minutes (range: 1-177). Fifty patients (10.5%) who underwent adhesiolysis

inadvertently incurred a bowel defect, compared to zero without adhesiolysis (P < 0.001). In univariate and multivariate analyses, adhesiolysis was associated with an increase of sepsis incidence [odds ratio (OR): 5.12; 95% confidence interval (CI): 1.06–24.71], intra-abdominal complications (OR: 3.46; 95% CI: 1.49–8.05) and wound infection (OR: 2.45; 95% CI: 1.01–5.94), longer hospital stay (2.06 ± 1.06 days), and higher hospital costs [$18,579 (15,204–21,954) vs $14,063 (12,471–15,655)]. Mortality after adhesiolysis complicated by a bowel defect was 4 out of 50 (8%), compared with 7 out of 425 (1.6%) after uncomplicated adhesiolysis (OR: 5.19; 95% CI: 1.47–18.41). Adhesiolysis and inadvertent bowel injury have a harmful effect on the convalescence after abdominal surgery.

The large negative impact of adhesiolysis during abdominal surgery on morbidity led to the hypothesis that adhesiolysis would impact quality of life as well. Therefore we prospectively collected data regarding quality of life and functional status in the LAPAD study by means of the Short-Form 36 (SF-36) and Duke's Activity Status Index (DASI) questionnaires. The results of this study are described in **Chapter 4**. 518 (78%) patients out of 662 were eligible for analysis and 319 patients required adhesiolysis during surgery. Postoperative quality of life did not significantly differ between both groups (p 0.12) and was not different from pre-operative values. Patients with adhesiolysis had a significantly lower pre- and postoperative functional status in comparison to these outcomes in patients not requiring adhesiolysis (p <0.01 and p <0.01). Higher age (p 0.05 and p <0.01), concomitant pulmonary disease (p 0.04 and p <0.01), postoperative Clavien-Dindo grade 4 complications (p <0.01 and p 0.05), readmissions within 30 days (p 0.01 and p <0.01), readmissions after 30 days (p <0.01 and p <0.01) and chronic abdominal pain 6 months after surgery (p <0.01 and p <0.01) were all associated with a significant and independent decline in quality of life and functional status six months after surgery. Patients requiring adhesiolysis have a lower pre- and postoperative functional status but adhesiolysis as such does not affect functional status and quality of life. Postoperative complications, readmissions and chronic abdominal pain are associated with a lower health status.

In the LAPAD study data regarding pain and pain-related factors was collected and because chronic postoperative abdominal pain (CPAP) showed to have a negative impact on quality of life we sought to assess risk factors for CPAP and gastrointestinal complaints and questioned if they relate to baseline adhesions in **Chapter 5**. Gastro-intestinal Symptom Rating Scale (GSRS) was used to assess gastrointestinal complaints. 184 (36%) of 518 patients included in the analysis had CPAP. The median GSRS score was 5 (IQR 3 – 10). The presence of pain either shorter (OR 2.69; p 0.016) or longer than three months (OR 3.99; p 0.000) before surgery, usage of

opioid analgesia preoperatively (OR 3.54; p 0.001), severe adhesions underneath the incision (OR 1.63; p 0.040) and a higher numeric pain rating scale value on post-operative day 2 (OR 1.23; p 0.004) showed to independently increase the risk for CPAP. Chronic pancreatitis as indication for surgery (B 4.20; p 0.03), 3 or more previous abdominal operations (B 1.03; p 0.03), presence of pain more than 3 months before surgery (B 1.61; p <0.01), upper gastrointestinal tract as the anatomical location of surgery (B 1.43; p 0.03) and a higher preoperative GSRS score (B 0.36; p <0.01) independently increased the GSRS score six months after surgery. The number of operations and the anatomical location of the operation showed to be important risk factors for increasing the number of gastrointestinal complaints. The duration and severity of preoperative pain and the presence of anxious and depressive symptoms were the most relevant risk factors for CPAP whereas adhesions and adhesiolysis related problems were not.

A median laparotomy is a common route in both acute and elective open general abdominal surgery. We used a large prospective patient cohort to investigate prolonged and difficult adhesiolysis in patients undergoing a repeat median laparotomy which is described in **Chapter 6**. Four or more previous laparotomies, a history or presence of an intra-peritoneal mesh, and the requirement of a complete midline incision were found to be independent risk factors for prolonged adhesiolysis through a median incision. The results of this study can be used to improve patient counselling, operating room strategy and choosing an entry method for the abdominal cavity at repeat surgery.

Given the increased morbidity when an iatrogenic enterotomy occurs in patients requiring adhesiolysis during surgery it is important to identify patients who are at risk for this complication. In **Chapter 7** we developed a prediction model, scoring the risk for inadvertent enterotomy based on preoperative factors. The number of previous laparotomies, anatomical site of the operation, presence of bowel fistula and laparotomy via a pre-existing median scar were independent predictors of bowel injury. A nomogram was constructed incorporating these four risk factors. The area under the receiver operating characteristic curve was 0.85. The predicted risk in a patient who has all four risk factors is 50%. It was concluded that the nomogram accurately predicts the risk for bowel injury and can readily be used to identify high risk patients.

Previous laparotomies lead to prolonged and difficult adhesiolysis and impact the incidence of adhesiolysis-related complications. It would be of interest to assess the impact of specific surgical factors during elective abdominal surgery on the incidence of repeat abdominal surgery in order to improve patient selection for using adhesive barriers. The large amount of prospectively collected peri-operative data of the

LAPAD study provided the opportunity to perform such a follow-up study. These results are presented in **Chapter 8**. Primary outcome was future repeat abdominal surgery and was defined as any operation where the peritoneal cavity is reopened. 604 (88%) out of 715 patients were included, median duration of follow-up was 46 months. 27% patients required repeat abdominal surgery within four years mostly due to malignant disease recurrence, incisional hernia and indications unrelated to the index surgery. The anatomical location of repeat surgery was most often the lower gastrointestinal tract and abdominal wall. Lower age, female sex and hepatic malignancy are significant risk factors for requiring repeat abdominal surgery.

The overall incidence of adhesive bowel obstruction is 2.4% in a systematic review and meta-analysis. The incidence is significantly higher after paediatric and lower gastrointestinal tract surgery, and lower after laparoscopic surgery in comparison to open surgery.[5] This data is derived from regional and national registries and retrospective cohorts of acute surgery for bowel obstruction and elective abdominal surgery. Due to the design of these studies it remains unknown whether specific surgical factors impact the occurrence of bowel obstruction. A follow-up study of the LAPAD enabled us to assess the impact of detailed surgical factors on the incidence of adhesive bowel obstruction in patients undergoing all types of elective abdominal surgery which is presented in **Chapter 9**. 604 patients were included and 6% of these patients developed an episode of adhesive bowel obstruction within 4 years. Surgery on the lower gastrointestinal tract and severe adhesions at the index operation increased the risk for adhesive bowel obstruction by 5 and 3 times, respectively. This study again demonstrated that adhesive bowel obstruction is a serious complication of colorectal surgery that needs to be routinely addressed by surgeons during informed consent.

A systematic review and meta-analysis showed that hyaluronate carboxymethylcellulose and oxidized regenerated cellulose safely reduce clinically relevant consequences of adhesions. The studies incorporated in this systematic review did not differentiate between patients with and without adhesions present at the index operation, and potentially underestimate the efficacy of adhesion barriers.[10, 11] In **Chapter 10** a systematic review on the prevention of adhesion reformation in animal models is presented providing translational data for the efficacy of adhesion barriers in reduction of adhesion reformation. Only 5% of all animal studies assessing adhesion prevention employed a model of adhesion reformation. Current commercially available adhesion barriers and laparoscopic adhesiolysis without using an adhesion barrier do not reduce the incidence of adhesion reformation in experimental animals. Overall, the methodological quality of animal studies was poor and there was great heterogeneity with regard to the animal models used for assessing the efficacy of adhesion barriers.

Chapter 11 provides a general discussion of the research presented in this thesis and future perspectives on adhesions related problems based on the adhesion 2.0 agenda.

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Appendices

Introductie

De publicaties van de 'SCAR studiegroep' eind vorige eeuw hebben adhesies (verklevingen) als belangrijkste oorzaak van complicaties na buikchirurgie op de kaart gezet en de wetenschappelijke interesse in de preventie van adhesies vergroot.[1-4] Recent is door ons een systematische review getiteld 'The burden of adhesions in abdominal and pelvic surgery' gepubliceerd waaruit blijkt dat adhesies grote medische en sociale gevolgen hebben voor patiënten die een buikoperatie ondergaan en de bijbehorende financiële kosten hoog zijn.[5] De vier meest voorkomende complicaties van adhesies zijn darm obstructie, de complicaties van het moeten losmaken van adhesies bij herhaaldelijke operaties in de buik (adhesiolyse), onvruchtbaarheid bij vrouwen en chronische buikpijn. In de afgelopen jaren is weinig vooruitgang geboekt in het voorkomen van adhesies. Dit komt mede door het gebrek aan kennis van artsen en beleidsmakers in de zorg over de negatieve gevolgen van adhesies. Uit een korte kennistoets blijkt dat de incidentie van adhesie gerelateerde complicaties door chirurgen en gynaecologen sterk wordt onderschat. Ook informeert minder dan 10% van deze specialisten hun patiënten routinematig over de risico's van adhesies voorafgaand aan een operatie.[6-8] Dit proefschrift heeft tot doel de kennis over de negatieve gevolgen van adhesies en adhesiolyse op postoperatieve uitkomsten te vergroten, risicofactoren voor het ontstaan van complicaties door adhesies in kaart te brengen en om passende zorg te bieden voor de patiënt die een buikoperatie ondergaat.

Hoofdstuk 1 bevat een introductie van dit proefschrift waarin de problematiek van adhesies bij herhaalde buikoperaties en als oorzaak van een darmobstructie en chronische pijn wordt samengevat. Tevens worden de verschillende studies van dit proefschrift hierin beschreven.

Hoofdstuk 2 geeft een uitgebreid overzicht van de huidige kennis over de ontstekingsreactie van het peritoneum (het buikvlies) wat het begin is van adhesievorming. Deze reactie kan in gang gezet worden door verschillende typen beschadiging van het peritoneum, waarvan chirurgisch trauma door een operatie de meest voorkomende is. Na een operatie, ongeacht het type, wordt een ontstekingsreactie op gang gebracht om het peritoneum te genezen. Deze ontstekingsreactie bestaat uit vier verschillende cascades, een immunologische, een humorale, een neurogene en een stollingscascade. Het uiteindelijke resultaat van deze cascades is meestal fibreus weefsel dat organen met elkaar en de buikwand verbind; dit zijn adhesies.

Uit een eerdere studie van onze groep is gebleken dat 19% van de patiënten, die opnieuw in de buik werden geopereerd, een enterotomie (onbedoelde perforatie van de darm) krijgen. Bij 54% van de patiënten met een enterotomie traden postoperatieve complicaties op. Postoperatieve complicaties traden op bij 35% van de patiënten

zonder enterotomie, dus aanzienlijk minder.[9] Gedetailleerde gegevens van patiënten en de uitgevoerde operaties waren niet voor handen in deze studie. De studie vormde de basis voor de LAParotomy or LAParoscopy and ADhesiolysis (LAPAD) studie, waarvan de resultaten zijn beschreven in **hoofdstuk 3**. De LAPAD studie is een groot prospectief cohortonderzoek met als doel de gevolgen van adhesiolyse en onopzettelijk orgaanletsel tijdens de operatie op postoperatieve uitkomsten nauwkeurig in kaart te brengen. In totaal waren 755 operaties bij 715 patiënten onderdeel van de studie, waarbij in 475 (62.9%) operaties adhesiolyse nodig was. De tijdsduur voor het losmaken van de adhesies verschilde van 1 tot 177 minuten en was mediaan 20 minuten. Bij vijftig patiënten (10.5%), waarbij tijdens de operatie adhesiolyse nodig was, ontstond een enterotomie. Dit aantal was 0 bij patiënten die geen adhesiolyse nodig hadden en dit verschil was significant, $P < 0.001$. In een multivariabele analyse was er een significante associatie tussen adhesiolyse en een toename van complicaties, waaronder sepsis (odds ratio (OR): 5.12; 95% betrouwbaarheid interval (CI): 1.06-24.71), intra-abdominale complicaties (OR: 3.46; 95% CI: 1.49-8.05), wondinfecties (OR: 2.45; 95% CI: 1.01-5.94); het aantal opname dagen (2.06 ± 1.06 dagen), en tussen adhesiolyse en hogere ziekenhuiskosten ($ 18.579 (15.204-21.954) ten opzichte van $ 14.063 (12.471-15.655)). De sterfte na een operatie waarbij adhesiolyse nodig was en een enterotomie ontstond was 8 procent vergeleken met 1.6 procent zonder ontstaan van een enterotomie (OR: 5.19; 95% CI: 1.47-18.41).
Wij concludeerden dat adhesiolyse met het optreden van een enterotomie negatieve gevolgen heeft op het herstel na buikchirurgie.

De gevonden negatieve gevolgen van adhesiolyse tijdens buikchirurgie op het postoperatieve herstel leidde tot de hypothese dat adhesiolyse ook de kwaliteit van het leven nadelig beïnvloedt. Daarom verzamelden we prospectief gegevens over kwaliteit van leven en het fysiek functioneren van patiënten in de LAPAD studie met behulp van de vragenlijsten Short Form 36 (SF-36) en Duke's Activity Status Index (DASI).
De resultaten van deze studie zijn beschreven in **hoofdstuk 4**. 518 van 662 (78%) patiënten konden worden geanalyseerd. Hiervan hadden 319 patiënten adhesiolyse nodig tijdens de operatie. De postoperatieve kwaliteit van leven verschilde niet significant tussen beide groepen (p 0.12) en verschilde ook niet van de preoperatieve kwaliteit van leven. Patiënten met adhesiolyse hadden een significant lagere pre- en postoperatieve score met betrekking tot het fysiek functioneren in vergelijking tot patiënten die geen adhesiolyse nodig hadden (p <0.01 en p <0.01). Een hogere leeftijd (p 0.05 en p <0.01), een chronische longaandoening in de voorgeschiedenis (p 0.04 en p <0.01), een ernstige postoperatieve complicatie (Clavien-Dindo graad 4) (p <0.01 en p 0.05), een heropname binnen 30 dagen (p 0.01 en p <0.01), een heropname na 30 dagen (p <0.01 en p <0.01) en chronische buikpijn zes maanden na de operatie (p <0.01 en p <0.01) hadden allemaal een significant en onafhankelijk

verband met de daling van de kwaliteit van leven en met het fysiek functioneren zes maanden na de operatie.
We concludeerden dat patiënten met adhesiolyse een lagere pre- en postoperatieve score hebben met betrekking tot het fysiek functioneren maar dat adhesiolyse geen onafhankelijke voorspeller is voor kwaliteit van leven en het fysiek functioneren na de operatie. Wel leiden ernstige postoperatieve complicaties, een heropname en chronische abdominale pijn, die alle drie vaker voorkomen na adhesiolyse, tot een lagere gezondheidsstatus zes maanden na buikchirurgie.

Uit hoofdstuk 4 blijkt dat chronische postoperatieve abdominale pijn (CPAP) ~~veel~~ optreedt en een verband heeft met een lagere kwaliteit van leven. Wij onderzochten in een vervolgstudie wat de risicofactoren zijn voor CPAP en andere gastro-intestinale klachten na een buikoperatie en of er een verband is tussen adhesies, adhesiolyse, chronische pijn en gastro-intestinale klachten. Deze studie is beschreven in **hoofdstuk 5**. De Gastro-intestinal Symptom Rating Scale (GSRS) werd gebruikt voor het in kaart brengen van de gastro-intestinale klachten. 184 (36%) van 518 patiënten hadden zes maanden na de operatie CPAP. De mediane GSRS score was 5 (Interquartile Range 3 - 10). De aanwezigheid van pijn korter (OR 2.69, p 0.016) of langer dan drie maanden (OR 3.99; p 0.000) voor de operatie, preoperatief gebruik van morfinomimetica (OR 3.54; p 0.001), zeer fibreuze adhesies onder de incisie (OR 1.63; P 0.040) en een hogere pijnscore op de tweede dag na de operatie (OR 1.23; p 0.004) gaven alle vijf een significant en onafhankelijk verhoogd risico op CPAP. Chronische pancreatitis als indicatie voor de operatie (B 4.20, p 0.03), drie of meer eerdere buikoperaties (B 1.03, p 0.03), aanwezigheid van pijn meer dan 3 maanden voor de operatie (B 1.61; p <0.01), het bovenste deel van het maagdarmkanaal als anatomische locatie van de operatie (B 1.43; p 0.03) en een hogere preoperatieve GSRS score (B 0.36; p <0.01) leidden tot een hogere GSRS score zes maanden na de operatie.
De duur en de ernst van pijn voor de operatie zijn de meest relevante risicofactoren voor het optreden van CPAP. Het aantal operaties en de anatomische locatie van de operatie zijn belangrijke risicofactoren voor gastro-intestinale klachten na een operatie. Adhesiolyse gerelateerde complicaties, zoals een enterotomie, hebben geen verband met het optreden van gastro-intestinale klachten of chronische buikpijn na de operatie.

Een mediane laparotomie is een veelgebruikte incisie voor zowel acute als electieve algemene buikchirurgie. We hebben een groot prospectief patiëntencohort gebruikt om langdurige en moeizame adhesiolyse te onderzoeken bij patiënten met een herhaalde mediane laparotomie. De resultaten hiervan zijn beschreven in **hoofdstuk 6**. Vier of meer voorgaande 'open' buikoperaties, het opnieuw (moeten) openen van de

hele mediane incisie en aanwezigheid of het aanwezig geweest zijn van een mesh in de buikholte bleken onafhankelijke risicofactoren te zijn voor een langdurige en moeizame adhesiolyse.
De resultaten van deze studie kunnen worden gebruikt om de preoperatieve informatie aan deze patiënten te verbeteren, bij het kiezen van de toegang tot de buik bij een volgende operatie en om de planning en logistiek van deze buikoperatie te optimaliseren.

Gezien de hoge morbiditeit bij patiënten met een iatrogene enterotomie door het losmaken of verwijderen van adhesies tijdens een operatie, is het belangrijk om het risico op een enterotomie vooraf in te kunnen schatten bij de individuele patiënt. Voor deze inschatting hebben we een voorspellingsmodel gecreëerd waarbij het risico op een iatrogene enterotomie is gebaseerd op preoperatief aanwezige gegevens, dit is beschreven in **hoofdstuk 7**. Het aantal eerdere buikoperaties, de anatomische plaats van de operatie, de aanwezigheid van een enterocutane fistel en een voorgaande operatie via een mediane incisie waren onafhankelijke voorspellers van een iatrogene enterotomie. Op basis van deze 4 risicofactoren is een nomogram gemaakt. De AUC (area under the operating characteristic curve) was 0,85 en het voorspelde risico bij een patiënt met alle vier de risicofactoren bedroeg 50%.
Het nomogram voorspelt nauwkeurig het risico op een iatrogene enterotomie en is een makkelijke tool om patiënten met een hoog risico op een enterotomie voorafgaand aan een buikoperatie te identificeren.

Eerdere buikoperaties kunnen leiden tot langdurige adhesiolyse bij een vervolgoperatie en houden verband met een verhoogde incidentie van adhesiolyse gerelateerde complicaties. Het is interessant om te kunnen voorspellen welke patiënten in de toekomst opnieuw een buikoperatie moeten ondergaan om bijvoorbeeld al bij de eerste buikoperatie middelen te gebruiken die adhesies voorkomen. De prospectief verzamelde en gedetailleerde data rondom de operatie in de LAPAD studie bood de gelegenheid om een follow-up studie uit te voeren waarbij werd gekeken of er voorspellers waren voor het opnieuw moeten ondergaan van een buikoperatie. De resultaten van deze follow-up studie zijn beschreven in **hoofdstuk 8**. De primaire studie uitkomst was de incidentie van buikchirurgie en werd gedefinieerd als iedere operatie waarbij de buikholte wordt heropend. 604 (88%) van de 715 patiënten uit de LAPAD studie konden worden geïncludeerd. De mediane duur van de follow-up was 46 maanden. 27% van de patiënten hadden opnieuw een buikoperatie nodig, hoofdzakelijk vanwege een recidief of metastase van de tumor waarvoor de originele buikoperatie was verricht, een littekenbreuk, maar ook voor indicaties die geen verband hielden met de voorgaande operatie. De anatomische locatie van de operaties in de follow-up betrof meestal de dunne of dikke darm en de buikwand. Een jongere leeftijd,

het vrouwelijk geslacht en een maligniteit van de lever waren de belangrijkste voorspellers voor het opnieuw moeten ondergaan van een buikoperatie binnen vier jaar.
Deze studie heeft resultaten opgeleverd die richting kunnen geven aan het efficiënt gebruik van maatregelen en middelen om adhesies en hieraan gerelateerde complicaties te voorkomen.

De gemiddelde incidentie van een darmobstructie veroorzaakt door adhesies is 2,4%. De incidentie is significant hoger na buikchirurgie op jonge leeftijd en operaties aan de dunne en dikke darm. De incidentie is lager na laparoscopische chirurgie in vergelijking met open buikoperaties.[5] Deze gegevens zijn afgeleid uit regionale en nationale registers en retrospectieve cohorten van electieve buikchirurgie en van acute operaties voor een darmobstructie. Door de aard van deze databases en het ontwerp van de studies kan niet worden onderzocht welke factoren tijdens de operatie het optreden van een darmobstructie in een latere fase beïnvloeden. In de LAPAD studie zijn deze gedetailleerde operatiegegevens wel verzameld en hebben we een follow-up studie verricht om te onderzoeken welke operatiefactoren het optreden van een darmobstructie door adhesies beïnvloeden. Dit is beschreven in **hoofdstuk 9**. Er werden 604 patiënten met een electieve buikoperatie geïncludeerd in deze studie. Hiervan had 6 procent binnen 4 jaar een of meerdere darmobstructies door adhesies doorgemaakt. Resecties van de dikke en/of de dunne darm en de aanwezigheid van ernstige verklevingen bij de voorgaande operatie verhoogden het risico op darmobstructie met respectievelijk 500 en 300 procent. Deze studie heeft opnieuw aangetoond dat darmobstructie door adhesies een ernstige lange termijn complicatie van abdominale chirurgie is die routinematig door chirurgen moet worden besproken met patiënten. Daarnaast kunnen de resultaten gebruikt worden om richting te geven aan het gebruik van middelen ter preventie van adhesies.

In een systematic review hebben we recent aangetoond dat twee anti-adhesie middelen (hyaluronate carboxymethylcellulose en oxidized regenerated cellulose) complicaties van adhesies verminderen zonder ernstige bijwerkingen. De studies die in deze systematische review zijn opgenomen maken geen onderscheid tussen patiënten waarbij adhesies wel of niet aanwezig zijn bij de operatie en dus of deze middelen de novo adhesies of opnieuw vorming van adhesies na het losmaken voorkomen (adhesie reformatie). Op pathofysiologische gronden is er reden om aan te nemen dat het voorkomen van adhesie reformatie moeilijker is dan het voorkomen van de novo adhesies.[10, 11] 40-60% van de buikoperaties bij mensen, in sommige ziekenhuizen, zijn heroperaties waarbij verklevingen aanwezig zijn. In **hoofdstuk 10** worden de resultaten van een systematische review en meta-analyse over de preventie van adhesie reformatie in diermodellen beschreven en is bestudeerd of de dierexperimentele data translationele waarde hebben voor de werkzaamheid van

preventieve middelen voor adhesie reformatie bij patiënten. Slechts in vijf procent van alle dierstudies die adhesiepreventie onderzochten werd een model van adhesie reformatie gebruikt. Huidige commercieel verkrijgbare middelen ter preventie van adhesies en het toepassen van laparoscopie bij het losmaken van de adhesies verminderden de aanwezigheid van opnieuw gevormde adhesies niet in deze diermodellen. De methodologische kwaliteit van de dierstudies was laag en er was veel heterogeniteit tussen de gebruikte diermodellen.
De conclusie is dat er vooralsnog geen dierexperimenteel bewijs is voor de werkzaamheid van bestaande anti-adhesie middelen om adhesie reformatie te voorkomen. Gezien de hoge prevalentie van heroperaties in de buik bevelen wij aan om ieder nieuw middel tegen adhesies te testen op preventie van adhesie reformatie in een klinisch relevant adhesiolyse model.

Hoofdstuk 11 betreft een algemene discussie over de klinische implicaties van de verschillende studies in dit proefschrift. Daarnaast worden de toekomstige doelen met betrekking tot onderzoek van adhesies en adhesie gerelateerde complicaties besproken op basis van onderstaande 'Adhesion 2.0' agenda.

Figure 1 De 'Adhesion 2.0' agenda.

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Curriculum Vitae

Chema Strik was born in Amsterdam on the 20th of June 1987. He grew up in Amsterdam and Megen, the Netherlands. After graduating from the Titus Brandsmalyceum in Oss in 2005 he started Medical School at the Radboud University Nijmegen the same year. After finishing his Bachelor of Science he worked for one year as a full-time researcher on the subject of peritoneal adhesions for professor H. van Goor at the Radboud University Medical Center. After completing Medical School in 2012 he went to prof. R.P. Bleichrodt at the Saint Francis' hospital in Zambia for a three month extra-curricular internship. Afterwards, he continued working for two years as a full-time researcher, resulting in this thesis. Chema worked as a medical doctor for one year at the departments of Emergency Medicine and General Surgery at the hospital Gelderse Vallei in Ede and for almost two years at the department of Intensive Care at the Rijnstate Hospital in Arnhem. He will start his residency in anesthesiology at the Radboud University Medical Center in January 2018 (dr. Keijzer-Broeders).

RIHS PhD portfolio

Institute for Health Sciences
Radboudumc

Name PhD candidate: C. Strik
Department: General Surgery
Graduate School: Radboud Institute for Health Sciences

PhD period: 01-11-2012 – 31-12-2014
Promotor(s): Prof. Dr. H. van Goor
Co-promotor(s): Dr. R.P.G. ten Broek

	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- Basiscursus Regelgeving en Organisatie van Klinische trials (BROK) Maastricht University	2013	1.0
- Hands-on training in synthesis of evidence in animal experimentation PAO- Heyendael – Nijmegen	2013	0.25
- Academic Writing Radboud University Nijmegen	2013	3.0
- Advanced Conversation Radboud University Nijmegen	2013	1.5
- Biometrics Radboud University Nijmegen	2013	6.0
- Radboud Institute for Health Sciences Introduction course for PhD students	2014	0.5
- Presentation Skills Radboud University Nijmegen	2013	1.5
- Laboratory animal science (artikel 9) Utrecht University	2014	3.0
b) Seminars & lectures		
- Consensus meeting Local & European Network Against Adhesions (oral presentation)	2014	0.5
- Radboud Research Round (oral presentation)	2017	0.1
c) Symposia & congresses ^		
- Chirurgendagen, Veldhoven	2013	0.5
- Chirurgendagen, Veldhoven	2014	0.5
- Tripartite colorectal meeting, Southampton (oral presentation)	2014	0.7
- Chirurgendagen, Veldhoven (oral presentation)	2015	0.5
- Digestive Disease Week, Washington DC, (2 poster presentations)	2015	1.2
d) Other		
- Researchmeeting department of surgery	2013-2014	1.0
TEACHING ACTIVITIES		
e) Lecturing		
- Assisted at the basic suturing course for interns every month		
- Assisted at various anatomy lectures and courses for interns and medical students		
f) Supervision of internships		
- LJ Schipper; 'Incidence of adhesion-related intestinal obstruction and relaparotomies three years after surgery in a prospective cohort'		
- JC Hol; 'Quality of life in patients requiring adhesiolysis during abdominal surgery'		
TOTAL		**21.75**

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